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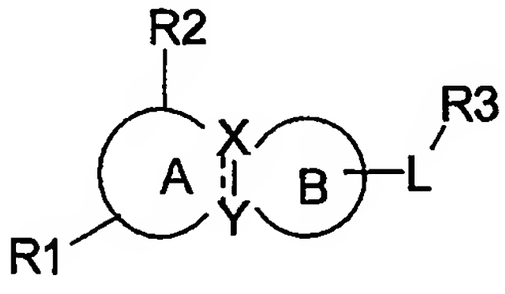
(54) Title: BICYCLIC COMPOUNDS AND THEIR THERAPEUTIC USE



(1)

(57) Abstract: Compounds of the formula (1) are useful as MCH mediator, and in the therapy of obesity.

BICYCLIC COMPOUNDS AND THEIR THERAPEUTIC USE

FIELD OF THE INVENTION

This invention relates to bicyclic compounds and their therapeutice use.

BACKGROUND OF THE INVENTION

Obesity, defined as excess adiposity for a given body size, results from a chronic imbalance between energy intake and energy expenditure. Body mass index (BMI, kg/m^2) is an accepted clinical estimate of being overweight (BMI 25 to 30) and of obesity (BMI>30). A BMI above 30 kg/m^2 significantly increases the risk of diabetes, hypertension, dyslipidemias and cardiovascular disease, gallstones, osteoarthritis and certain forms of cancer and reduces life expectancy.

In the vast majority of obese individuals, the cause of the excess adiposity is not immediately apparent. A currently accepted working hypothesis is that obesity is the result of maladaptation of the innate metabolic response to environmental challenges such as unlimited availability of low cost/energy dense foods and sedentariness (Hill *et al.*, *Science*, **1998**, *280*, 1371). The study of energy intake in free living humans has met with only limited success and definitive experimental evidence that hyperphagia causes most forms of human obesity is lacking. Following the discovery of leptin, the interest in the neurohormonal regulation of food intake has regained momentum. However, while much knowledge has been gained on the regulation of food intake in rodents and other animal species, the understanding of the neurophysiology of feeding behaviour in humans remains extremely limited.

Neuropeptides present in the hypothalamus play a major role in mediating the control of body weight (Flier, *et al., Cell,* **1998,** *92,* 437 – 440). Melanin–concentrating hormone (MCH) is a cyclic 19 amino acid neuropeptide synthesized as part of a larger pre–prohormone precursor in the hypothalamus which also encodes neuropeptides NEI and NGE. (Nahon, *et al., Mol. Endocrinol.* **1990,** *4,* 632–637). MCH was first identified in salmon pituitary and MCH affects melanin aggregation in fish thus affecting skin pigmentation. In

trout and in eels MCH has also been shown to be involved in stress induced or CRF–stimulated ACTH release (Kawauchi, *et al., Nature,* **1983** *305*, 321-323).

In humans two genes encoding MCH have been identified that are expressed in the brain. (Brecton, *et al., Mol. Brain Res.* **1993**, *18,* 297 – 310). In mammals MCH has been localized primarily to neuronal cell bodies of the hypothalamus which are implicated in the control of food intake, including perikayra of the lateral hypothalamus and zona inertia. (Knigge, *et al., Peptides,* **1996,** *17,* 1063 –1073.)

Pharmacological and genetic evidence suggest that the primary mode of MCH action is to promote feeding (orexigenic). MCH mRNA is up–regulated in fasted mice and rats, in the *ob/ob* mouse and in mice with targeted disruption in the gene for neuropeptide Y (NPY). (Qu, *et al., Nature,* **1996**, *380,* 243 – 247, and Erickson, *et al., Nature* **1996**, *381*, 415 – 418). Injection of MCH intracerebroventricularly (ICV) stimulates food intake and MCH antagonizes the hypophagic effects seen with a melanocyte-stimulating hormone (aMSH). (Qu, et al., *Nature, **1996**, 380,* 243 – 247). MCH deficient mice are lean, hypophagic and have increased metabolic rate. (Shimada, *et al., Nature* **1998,** *396,* 670 – 673).

MCH action is not limited to modulation of food intake as effects on the hypothalamic–pituitary-axis have been reported. (Nahon, *Critical Rev. in Neurobiol.* **1994,** *8,* 221 – 262.) MCH may be involved in the body's response to stress as MCH can modulate the stress-induced release of CRF from the hypothalamus and ACTH from the pituitary.

In addition, MCH neuronal systems may be involved in reproductive or maternal function. MCH transcripts and MCH peptide were found within germ cells in testes of adult rats, suggesting that MCH may participate in stem cell renewal and/or differentiation of early spermatocytes (Hervieu *et al.*, 1996). MCH injected directly into the medial preoptic area (MPOA) or ventromedial nucleus (VMN) stimulated sexual activity in female rats (Gonzalez *et al.*, 1996). In ovariectomized rats primed with estradiol, MCH stimulated luteinizing hormone (LH) release while anti-MCH antiserum inhibited LH release (Gonzalez *et al.*, 1997). The zona incerta, which contains a large population of MCH cell bodies,

has previously been identified as a regulatory site for the pre-ovulatory LH surge (MacKenzie *et al.*, 1984). Therefore modulators of MCH receptors may be useful in the prevention and treatment of reproductive function. MCH has been reported to influence release of pituitary hormones including ACTH and oxytocin. Therefore, modulators of MCH receptors may be useful in the prevention and treatment of obesity, Cushing's disease, sexual function, appetite and eating disorders, obesity, diabetes, cardiovascular disease, hypertension, dyslipidemia, myocardial infarction, gall stones, osteoarthritis, certain cancers, AIDS wasting, cachexia, frailty (particularly in the elderly), binge eating disorders including bulimia, anorexia, kidney function, diuresis, reproductive function and sexual function.

Two receptor subtypes have been identified in humans, MCH-1R and MCH-2R. Both receptors, as well as the gene for the MCH peptide, have been mapped to regions previously reported to contain a susceptibility gene for psychiatric disorders. In particular, MCH-1R was mapped to chromosome 22q13.2 (Kolakowski *et al.* 1996). The possibility of linkage for schizophrenia susceptibility locus in theis area was suggested by independent studies from 2 groups (Pulver *et al.* 1994; Coon *et al.* 1994). In addition, a more recent study (Stoeber *et al.* 2000) of samples from patients with periodic catatonia, a clinical subtype of unsystematic schizophrenia, suggested possible linkage of the region around 22q13. Human genetics implicates these loci not only for schizophrenia but also for bipolar disorder. The second MCH receptor (MCH-2R) has been mapped to chromosome 6q16.2-16.3 (Sailer *et al.*, 2001). Cao *et al.* (1997) were the first to report evidence of a schizophrenia susceptibility locus in that area. This initial report was confirmed and extended by other reports (Martinez *et al.* 1999; Kaufmann *et al.* 1998; Levinson *et al.* 2000). Schizophrenia has been recognised as a disorder with profound deficits in information-processing and attentional abnormalities. One of the few possible paradigms available to assess these types of deficits in information processing is sensory gating, a filtering process which can be demonstrated by using a paired auditory stimulus. Miller *et al.* (1993) examined the effects of ICV administered MCH on the decrease in amplitude of the second of two tone-evoked CNS potentials that can be

measured when pairs of identical tones are presented 500ms apart. They found that MCH application decreases sensory gating in this paradigm. Based on pathogenesis and pathophysiology (reviewed in Lewis and Libermann, 2000) several brain areas have been implicated in schizophrenia, all of which show high expression for MCH receptors: thalamus, midbrain, nucleus accumbens, temporo-limbic, and prefrontal cortices. These studies and findings support the use of MCH receptor modulators in the treatment and prevention of schizophrenia.

Kelsoe *et al.* (2001) recently reported on a genome survey indicating a possible susceptibility locus for bipolar disorder identified on 22q. The MCH gene which encodes the MCH pro-peptide was mapped to chromosome 12q23.1. This area has been identified by Morissette *et al.* (1999) in a genome wide scan for susceptibility loci for bipolar disorder in families in the Province of Quebec. In addition, Ewald *et al.* (1998) showed significant linkage to chromosome 12q23.1 (maximum lod score 3.37) in Danish families suffering from bipolar affective disorder. In addition, Presse *et al.* (1997) have shown that lithium, the "gold standard" and most appropriate initial treatment for the depressive phase of bipolar disorder, can alter MCH mRNA levels in NGF-treated PC12 cells by increasing mRNA stability. These studies and findings support the use of MCH receptor modulators in the treatment and prevention of bipolar disorder and depression.

Philippe and colleagues (1999) performed a genome-wide screen for a autism susceptibility gene and found suggestive linkage for the region of chromosome 6q16.1-16.3 (maximum lod score 2.23). This finding supports the use of MCH receptor modulators in the treatment of autism.

In all species studied to date, a major portion of the neurons of the MCH cell group occupies a rather constant location in those areas of the lateral hypothalamus and subthalamus where they lie and may be a part of some of the so-called "extrapyramidal" motor circuits. These involve substantial striato-and pallidofugal pathways involving the thalamus and cerebral cortex, hypothalamic areas, and reciprocal connections to subthalamic nucleus, substantia nigra, and mid-brain centres (Bittencourt *et al.*, 1992). In their location, the MCH cell group

may offer a bridge or mechanism for expressing hypothalamic visceral activity with appropriate and coordinated motor activity. Thus, modulators of MCH receptor function may be useful in the treatment and prevention of movement disorders, such as Parkinson's disease, Parkinson-like syndromes and Huntingdon's Chorea in which extrapyramidal circuits are known to be involved.

Human genetic linkage studies have located authentic hMCH loci on chromosome 12 (12q23-24) and the variant hMCH loci on chromosome 5 (5q12-13) (Pedeutour *et al.*, 1994). Locus 12q23-24 coincides with a locus to which autosomal dominant cerebellar ataxia type II (SCA2) has been mapped (Auburger *et al.*, 1992; Twells *et al.*, 1992). This disease comprises neurodegenerative disorders, including an olivopontocerebellar atrophy. Furthermore, the gene for Darier's disease, has been mapped to locus 12q23-24 (Craddock *et al.*, 1993). Darier's disease is characterized by abnormalities in keratinocyte adhesion and mental illnesses in some families. In view of the functional and neuroanatomical patterns of the MCH neural system in the rat and human brains, the MCH gene may represent a good candidate for SCA2 or Darier's disease. Therefore, modulators of MCH receptors may be useful in the treatment of mental disorders including manic depression, depression, schizophrenia, mood disorders, delirium, dementia, severe mental retardation, anxiety, stress, cognitive disorders, and dyskinesias including Parkinson's disease, Tourette's syndrome, Huntington's disease, cerebellar ataxia, and seizures.

Further, the gene responsible for chronic or acute forms of spinal muscular atrophies has been assigned to chromosome 5q12-13 using genetic linkage analyses (Melki *et al.*, 1990; Westbrook *et al.*, 1992). Therefore, modulators of MCH receptors may be useful in treating muscular dystrophy and dyskinesias, including Parkinson's disease, Tourette's syndrome, Huntington's disease, cerebellar ataxia, seizures, locomotor disorders, attention deficit disorder (ADD) and substance abuse disorders.

Still further, modulators of MCH receptor binding may also be useful in treating epilepsy. In the PTZ seizure model, injection of MCH prior to seizure induction prevented seizure activity in both rats and guinea pigs, suggesting that

MCH-containing neurons may participate in the neural circuitry underlying PTZ-induced seizure (Knigge and Wagner, 1997). MCH has also been observed to affect behavioural correlates of cognitive functions. MCH treatment hastened extinction of the passive avoidance responses in rats (McBride *et al.*, 1994), raising the possibility that MCH receptor antagonists may be beneficial for memory storage and/or retention.

A role for MCH in the modulation or perception of pain is supported by the dense innervation of the periaqueductal grey (PAG) by MCH-positive fibers. MCH receptor modulators may be useful as antinociceptives or as analgesics, particularly for the treatment of neuropathic pain.

Finally, MCH may participate in the regulation of fluid intake. ICV infusion of MCH in conscious sheep produced diuretic, natriuretic, and kaliuretic changes in response to increased plasma volume (Parkes, 1996). Together with anatomical data reporting the presence of MCH in fluid regulatory areas of the brain, the results indicate that MCH may be an important peptide involved in the central control of fluid homeostasis in mammals. Therefore, modulators of MCH receptors may be useful in kidney function and diuresis.

Several antagonists of MCH-1R have been reported (Carpenter and Hertzog, *Expert Opin. Ther. Patents*, **2002**, 12, 1639-1646; Collins and Kym, *Curr. Opin. Invest. Drugs*, **2003**, 4, 386-394; Takekawa *et al., Eur. J. Pharmacol.*, **2002**, 438, 129-135; Borowsky *et al., Nature Medicine*, **2002**, 8, 825-830).

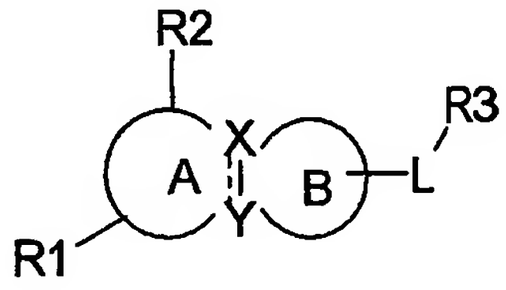
SUMMARY OF THE INVENTION

It is an object of the current invention to provide novel antagonists of the MCH-1R receptor.

The compounds of the present invention are modulators of the MCH–1R receptor and are useful in the treatment, prevention and suppression of diseases mediated by the MCH–1R receptor. The invention is concerned with the use of these novel compounds to selectively antagonize the MCH–1R receptor. As such, compounds of the present invention are useful for the treatment or prevention of obesity, diabetes, appetite and eating disorders, cardiovascular disease, hypertension, dyslipidemia, myocardial infarction, gall stones, osteoarthritis, certain cancers, AIDS wasting, cachexia, frailty (particularly in the

elderly), binge eating disorders including bulimina, anorexia, mental disorders including manic depression, depression, schizophrenia, mood disorders, delirium, dementia, severe mental retardation, anxiety, stress, cognitive disorders, sexual function, reproductive function, kidney function, diuresis, locomotor disorders, attention deficit disorder (ADD), substance abuse disorders and dyskinesias including Parkinson's disease, Parkinson–like syndromes, Tourette's syndrome, Huntington's disease, epilepsy, improving memory function, and spinal muscular atrophy.

This invention provides compounds of formula (1)

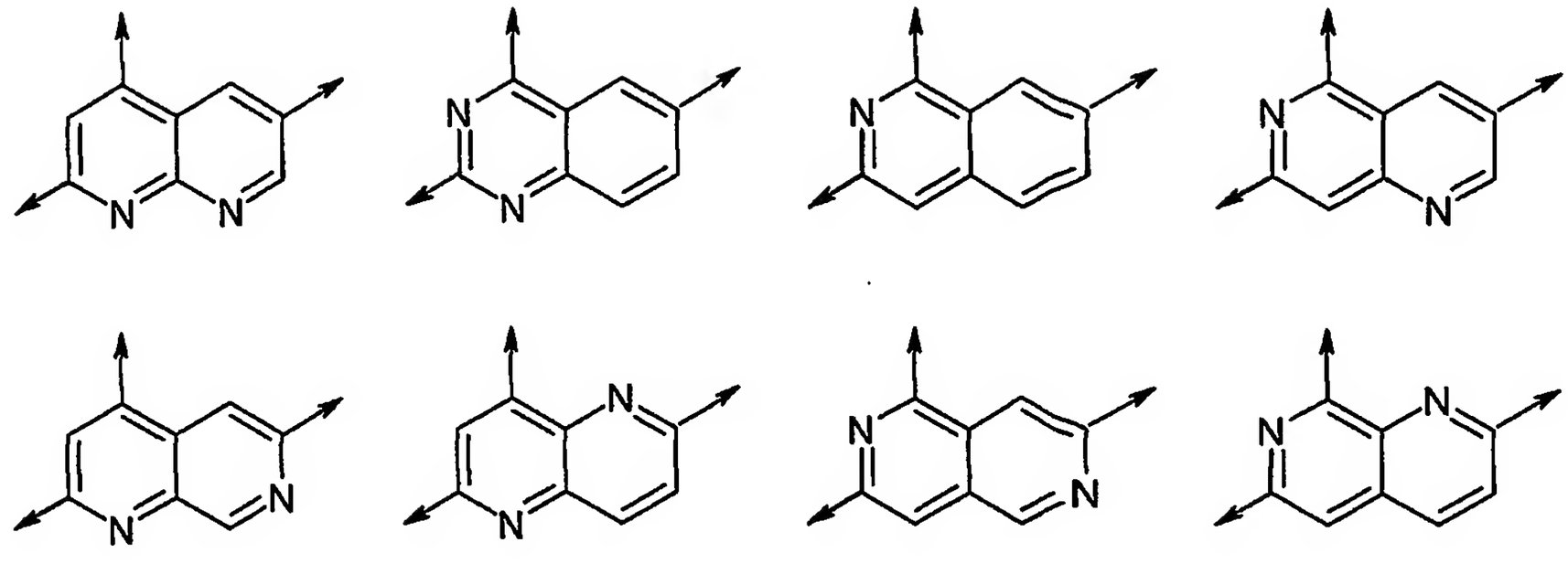


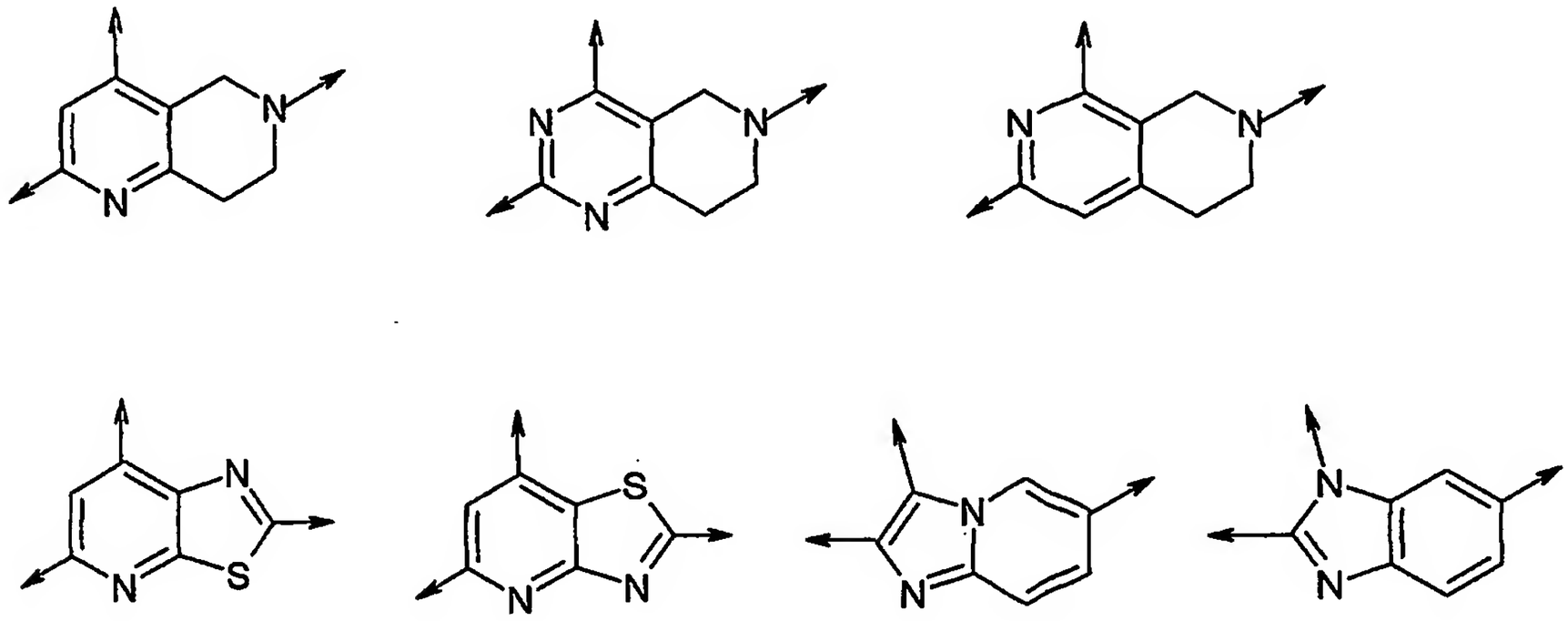
(1)

X and Y each independently represent N or C;

---- represents a single or double bond

Suitable ring systems represented by formula (1) include, but are not limited to, the following, wherein the arrows indicate the position of attachment of the substituents:





R1 represents NR4R5 or optionally substituted aryl, heteroaryl, aryl-fused-cycloalkyl, heteroaryl-fused-cycloalkyl, aryl-fused-heterocycloalkyl, heteroaryl-fused-heterocycloalkyl;

R2 represents H, R6, alkyl, or alkyl-R6;

R4 and R5, which may be the same or different, each independently represents H, alkyl, alkyl-R12, optionally substituted cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl or NR4R5 may form an optionally substituted cyclic amine;

R6 represents halogen, CN, CONR7R8, SO_2NR7R8, OR9, NR7R8, NR7COR10, NR7SO_2R10, NR7CONR7R8;

R7 and R8, which may be the same or different, each independently represent H, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl;

R9 represents H, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl;

R10 represents alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl;

R3 represents optionally substituted aryl, heteroaryl, aryl-fused-cycloalkyl, heteroaryl-fused-cycloalkyl, aryl-fused-heterocycloalkyl, heteroaryl-fused-heterocycloalkyl;

L represents $-(CH_2)_nCON(R11)(CH_2)_m-$, $-(CH_2)_nSO_2N(R11)(CH_2)_m-$, $-(CH_2)_nCON(R11)(CH_2)_rO-$, $-(CH_2)_nSO_2N(R11)(CH_2)_rO-$, $-(CH_2)_nCON(R11)(CH_2)_rS-$, $-(CH_2)_nSO_2N(R11)(CH_2)_rS-$, $-(CH_2)_nCON(R11)(CH_2)_rN(R11)-$, $-(CH_2)_nSO_2N(R11)(CH_2)_rN(R11)-$, $-(CH_2)_nN(R11)CO(CH_2)_m-$, $-(CH_2)_nN(R11)SO_2(CH_2)_m-$, $-(CH_2)_nN(R11)CO(CH_2)_mO(CH_2)_p-$, $-(CH_2)_nN(R11)SO_2(CH_2)_mO(CH_2)_p-$, $-(CH_2)_nN(R11)CO(CH_2)_mS(CH_2)_p-$, $-(CH_2)_nN(R11)SO_2(CH_2)_mS(CH_2)_p-$, $-(CH_2)_nN(R11)CO(CH_2)_mN(R11)(CH_2)_p-$, $-(CH_2)_nN(R11)SO_2(CH_2)_mN(R11)(CH_2)_p-$, $-(CH_2)_nO(CH_2)_m-$, $-(CH_2)_nS(CH_2)_m-$, $-(CH_2)_nN(R11)(CH_2)_m-$, $-(CH_2)_nCO(CH_2)_m-$, $-(CH_2)_nSO_2(CH_2)_m-$, $-(CH_2)_q-$, $-(CH_2)_nCO(CH_2)_mO(CH_2)_p-$, $-(CH_2)_nSO_2(CH_2)_mO(CH_2)_p-$, $-(CH_2)_nCO(CH_2)_mS(CH_2)_p-$, $-(CH_2)_nSO_2(CH_2)_mS(CH_2)_p-$, $-(CH_2)_nCO(CH_2)_mN(R11)(CH_2)_p-$, $-(CH_2)_nSO_2(CH_2)_mN(R11)(CH_2)_p-$, $-(CH_2)_n$-cycloalkyl-$(CH_2)_m-$, $-(CH_2)_n$-heterocycloalkyl-$(CH_2)_m$, $-(CH_2)_n$-aryl-$(CH_2)_m-$, $-(CH_2)_n$-heteroaryl-$(CH_2)_m-$, in each case, the linker may be attached either way round, i.e. the left hand end as drawn may be attached to the ring system and the right hand end to R3, or vice versa;

R11 represents H or alkyl;

R12 represents halogen, CN, CONR7R8, SO_2NR7R8, OR9, NR7R8, NR7COR10, NR7SO_2R10, NR7CONR7R8;

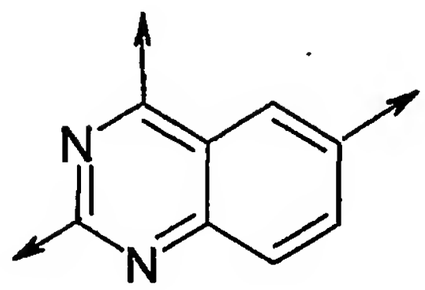
n, m and p each independently represent 0, 1 or 2;

q represents 0,1, 2, 3, 4 or 5;

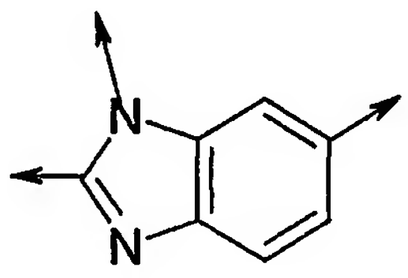
r represents 2 or 3;

and corresponding N-oxides, pharmaceutically acceptable salts, solvates and prodrugs of such compounds.

In one embodiment, the ring system represented by formula (1) is a quinazoline, i.e.



In another embodiment, the ring system represented by formula (1) is a benzimidazole, i.e.



In the same or another embodiment, R1 represents NR4R5.

In an alternative embodiment, R1 represents an optionally substituted heteroaryl group attached to the ring system via a carbon atom. Suitable representative heteroaryl groups include pyridyl, furanyl, imidazolyl and pyrazolyl.

In an alternative embodiment, R1 represents an optionally substituted heteroaryl group attached to the ring system via a nitrogen atom. A suitable representative heteroaryl group is imidazolyl.

In the same or another embodiment, R2 represents alkyl or haloalkyl, especially alkyl, particularly methyl.

In the same or another embodiment, R3 preferably represents a phenyl group substituted in the para position by a suitable substituent. Suitable substituents include haloalkyl, especially trifluoromethyl.

In the same or another embodiment, L represents $-(CH_2)_nN(R11)CO(CH_2)_mO(CH_2)_p-$, in which n and p preferably represent 0 and m preferably represents 1. In an alternative embodiment, L represents

-$(CH_2)_nN(R11)CO(CH_2)_m$- in which n represents 0 and m represents 2. In both embodiments, R11 preferably represents H. In both embodiments, L is attached as written, i.e. the left hand end is attached to the ring system and the right hand end is attached to R3.

As MCH-1R antagonists, the compounds of the present invention may be useful in treating the following conditions: obesity, diabetes, appetite and eating disorders, cardiovascular disease, hypertension, dyslipidemia, myocardial infarction, gall stones, osteoarthritis, certain cancers, AIDS wasting, cachexia, frailty (particularly in the elderly), binge eating disorders including bulimina, anorexia, mental disorders including manic depression, depression, schizophrenia, mood disorders, delirium, dementia, severe metal retardation, anxiety, stress, cognitive disorders, sexual function, reproductive function, kidney function, diuresis, locomotor disorders, attention deficit disorder (ADD), substance abuse disorders and dyskinesias including Parkinson's disease, Parkinson-like syndromes, Tourette's syndrome, Huntingdon's disease, epilepsy, improving memory function, and spinal muscular atrophy.

The present invention is also concerned with treatment of these conditions, and the use of compounds of the present invention for manufacture of a medicament useful in treating these conditions.

The invention is also concerned with pharmaceutical formulations comprising one of the compounds as an active ingredient.

The invention is further concerned with processes for preparing the compounds of this invention.

DESCRIPTION OF THE INVENTION

For purposes of the present invention, the following chemical terms as used above, and throughout the description of the invention, and unless otherwise indicated, shall be understood to have the following meanings:

"Acyl" means a -CO-alkyl group in which the alkyl group is as described herein. Exemplary acyl groups include $-COCH_3$ and $-COCH(CH_3)_2$.

"Acylamino" means a -NR-acyl group in which R and acyl are as described herein. Exemplary acylamino groups include $-NHCOCH_3$ and $-N(CH_3)COCH_3$.

"Alkoxy" and "alkyloxy" means an -O-alkyl group in which alkyl is as defined below. Exemplary alkoxy groups include methoxy and ethoxy.

"Alkoxycarbonyl" means a -COO-alkyl group in which alkyl is as defined below. Exemplary alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl.

"Alkyl" as a group or part of a group refers to a straight or branched chain saturated hydrocarbon group having from 1 to 12, preferably 1 to 6, carbon atoms in the chain. Exemplary alkyl groups include methyl, ethyl, 1 -propyl and 2-propyl.

"Alkylamino" means a -NH-alkyl group in which alkyl is as defined above. Exemplary alkylamino groups include methylamino and ethylamino.

"Alkylsufinyl" means a -SO-alkyl group in which alkyl is as defined above. Exemplary alkylsulfinyl groups include methylsulfinyl and ethylsulfinyl.

"Alkylsufonyl" means a $-SO_2$-alkyl group in which alkyl is as defined above. Exemplary alkylsulfonyl groups include methylsulfonyl and ethylsulfonyl.

"Alkylthio" means a -S-alkyl group in which alkyl is as defined above. Exemplary alkylthio groups include methylthio and ethylthio.

"Aminoacyl" means a -CO-NRR group in which R is as herein described. Exemplary aminoacyl groups include $-CONH_2$ and $-CONHCH_3$.

"Aminoalkyl" means an alkyl-NH_2 group in which alkyl is as previously described. Exemplary aminoalkyl groups include $-CH_2NH_2$.

"Aminosulfonyl" means a $-SO_2$-NRR group in which R is as herein described. Exemplary aminosulfonyl groups include $-SO_2NH_2$ and $-SO_2NHCH_3$.

"Aryl" as a group or part of a group denotes an optionally substituted monocyclic or multicyclic aromatic carbocyclic moiety of from 6 to 14 carbon atoms, preferably from 6 to 10 carbon atoms, such as phenyl or naphthyl, and in one embodiment preferably phenyl. The aryl group may be substituted by one or more substituent groups.

"Arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl moieties are as previously described. Preferred arylalkyl groups contain a C1-4 alkyl moiety. Exemplary arylalkyl groups include benzyl, phenethyl and naphthlenemethyl.

"Arylalkyloxy" means an aryl-alkyloxy- group in which the aryl and alkyloxy moieties are as previously described. Preferred arylalkyloxy groups contain a C1-4 alkyl moiety. Exemplary arylalkyl groups include benzyloxy.

"Aryl-fused-cycloalkyl" means a monocyclic aryl ring, such as phenyl, fused to a cycloalkyl group, in which the aryl and cycloalkyl are as described herein. Exemplary aryl-fused-cycloalkyl groups include tetrahydronaphthyl and indanyl. The aryl and cycloalkyl rings may each be sustitued by one or more substituent groups. The aryl-fused-cycloalkyl group may be attached to the remainder of the compound of formula (1) by any available carbon atom.

"Aryl-fused-heterocycloalkyl" means a monocyclic aryl ring, such as phenyl, fused to a heterocycloalkyl group, in which the aryl and heterocycloalkyl are as described herein. Exemplary aryl-fused-heterocycloalkyl groups include tetrahydroquinolinyl, indolinyl, benzodioxinyl, benxodioxolyl, dihydrobenzofuranyl and isoindolonyl. The aryl and heterocycloalkyl rings may each be sustitued by one or more substituent groups. The aryl-fused-heterocycloalkyl group may be attached to the remainder of the compound of formula (1) by any available carbon or nitrogen atom.

"Aryloxy" means an -O-aryl group in which aryl is described above. Exemplary aryloxy groups include phenoxy.

"Cyclic amine" means an optionally substituted 3 to 8 membered monocyclic cycloalkyl ring system where one of the ring carbon atoms is replaced by nitrogen, and which may optionally contain an additional heteroatom selected from O, S or NR (where R is as described herein). Exemplary cyclic amines include pyrrolidine, piperidine, morpholine, piperazine and N-methylpiperazine. The cyclic amine group may be substituted by one or more substituent groups.

"Cycloalkyl" means an optionally substituted saturated monocyclic or bicyclic ring system of from 3 to 12 carbon atoms, preferably from 3 to 8 carbon atoms, and more preferably from 3 to 6 carbon atoms. Exemplary monocyclic cycloalkyl rings include cyclopropyl, cyclopentyl, cyclohexyl and cycloheptyl. The cycloalkyl group may be substituted by one or more substituent groups.

"Cycloalkylalkyl" means a cycloalkyl-alkyl- group in which the cycloalkyl and alkyl moieties are as previously described. Exemplary monocyclic cycloalkylalkyl groups include cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl and cycloheptylmethyl.

"Dialkylamino" means a -N(alkyl)$_2$ group in which alkyl is as defined above. Exemplary dialkylamino groups include dimethylamino and diethylamino.

"Halo" or "halogen" means fluoro, chloro, bromo, or iodo. Preferred are fluoro or chloro.

"Haloalkoxy" means an -O-alkyl group in which the alkyl is substituted by one or more halogen atoms. Exemplary haloalkyl groups include trifluoromethoxy and difluoromethoxy.

"Haloalkyl" means an alkyl group which is substituted by one or more halo atoms. Exemplary haloalkyl groups include trifluoromethyl.

"Heteroaryl" as a group or part of a group denotes an optionally substituted aromatic monocyclic or multicyclic organic moiety of from 5 to 14 ring atoms, preferably from 5 to 10 ring atoms, in which one or more of the ring atoms is/are element(s) other than carbon, for example nitrogen, oxygen or sulfur. Examples of such groups include benzimidazolyl, benzoxazolyl, benzothiazolyl, benzofuranyl, benzothienyl, furyl, imidazolyl, indolyl, indolizinyl, isoxazolyl, isoquinolinyl, isothiazolyl, oxazolyl, oxadiazolyl, pyrazinyl, pyridazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, tetrazolyl, 1,3,4-thiadiazolyl, thiazolyl, thienyl and triazolyl groups. The heteroaryl group may be substituted by one or more substituent groups. The heteroaryl group may be attached to the remainder of the compound of formula (1) by any available carbon or nitrogen atom.

"Heteroarylalkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl moieties are as previously described. Preferred heteroarylalkyl groups contain a lower alkyl moiety. Exemplary heteroarylalkyl groups include pyridylmethyl.

"Heteroarylalkyloxy" means a heteroaryl-alkyloxy- group in which the heteroaryl and alkyloxy moieties are as previously described. Preferred

heteroarylalkyloxy groups contain a lower alkyl moiety. Exemplary heteroarylalkyloxy groups include pyridylmethyloxy.

"Heteroaryloxy" means a heteroaryloxy- group in which the heteroaryl is as previously described. Exemplary heteroaryloxy groups include pyridyloxy.

"Heteroaryl-fused-cycloalkyl" means a monocyclic heteroaryl group, such as pyridyl or furanyl, fused to a cycloalkyl group, in which heteroaryl and cycloalkyl are as previously described. Exemplary heteroaryl-fused-cycloalkyl groups include tetrahydroquinolinyl and tetrahydrobenzofuranyl. The heteroaryl and cycloalkyl rings may each be sustitued by one or more substituent groups. The heteroaryl-fused-cycloalkyl group may be attached to the remainder of the compound of formula (1) by any available carbon or nitrogen atom.

"Heteroaryl-fused-heterocycloalkyl" means a monocyclic heteroaryl group, such as pyridyl or furanyl, fused to a heterocycloalkyl group, in which heteroaryl and heterocycloalkyl are as previously described. Exemplary heteroaryl-fused-heterocycloalkyl groups include dihydrodioxinopyridinyl, dihydropyrrolopyridinyl, dihydrofuranopyridinyl and dioxolopyridinyl. The heteroaryl and heterocycloalkyl rings may each be sustitued by one or more substituents groups. The heteroaryl-fused-heterocycloalkyl group may be attached to the remainder of the compound of formula (1) by any available carbon or nitrogen atom.

"Heterocycloalkyl" means: (i) an optionally substituted cycloalkyl group of from 4 to 8 ring members which contains one or more heteroatoms selected from O, S or NR; (ii) a cycloalkyl group of from 4 to 8 ring members which contains CONR and CONRCO (examples of such groups include succinimidyl and 2-oxopyrrolidinyl). The heterocycloalkyl group may be substituted by one or more substituent groups. The heterocycloalkyl group may be attached to the remainder of the compound of formula (1) by any available carbon or nitrogen atom.

"Heterocycloalkylalkyl" means a heterocycloalkyl-alkyl- group in which the heterocycloalkyl and alkyl moieties are as previously described.

"Lower alkyl" as a group means unless otherwise specified, an aliphatic hydrocarbon group which may be straight or branched having 1 to 4 carbon

atoms in the chain, i.e. methyl, ethyl, propyl (n-propyl or i-propyl) or butyl (n-butyl, i-butyl or t-butyl).

"R" means hydrogen, alkyl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroarylalkyl, heteroaryl or aryl.

"Sulfonyl" means a $-SO_2$-alkyl group in which alkyl is as described herein. Exemplary sulfonyl groups include methanesulfonyl.

"Sulfonylamino" means a -NR-sulfonyl group in which R and sulfonyl are as described herein. Exemplary sulfonylamino groups include $-NHSO_2CH_3$.

"Prodrug" means a compound which is convertible in vivo by metabolic means (e.g. by hydrolysis, reduction or oxidation) to a compound of formula (1). For example an ester prodrug of a compound of formula (1) containing a hydroxy group may be convertible by hydrolysis in vivo to the parent molecule. Suitable esters of compounds of formula (1) containing a hydroxy group, are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-b-hydroxynaphthoates, gentisates, isethionates, di-p-toluoyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quinates. As another example an ester prodrug of a compound of formula (1) containing a carboxy group may be convertible by hydrolysis in vivo to the parent molecule [Examples of ester prodrugs are those described by F. J. Leinweber, Drug Metab. Res., 18:379 (1987)].

"Saturated" pertains to compounds and/or groups which do not have any carbon-carbon double bonds or carbon-carbon triple bonds.

The cyclic groups referred to above, namely, aryl, heteroaryl, cycloalkyl, aryl-fused-cycloalkyl, heteroaryl-fused-cycloalkyl, heterocycloalkyl, aryl-fused-heterocycloalkyl, heteroaryl-fused-heterocycloalkyl and cyclic amine may be substituted by one or more substituent groups. Suitable optional substituent groups include acyl (e.g. $-COCH_3$), alkoxy (e,g, $-OCH_3$), alkoxycarbonyl (e.g. $-COOCH_3$), alkylamino (e.g. $-NHCH_3$), alkylsulfinyl (e.g. $-SOCH_3$), alkylsulfonyl (e.g. $-SO_2CH_3$), alkylthio (e.g. $-SCH_3$), $-NH_2$, aminoalkyl (e.g. $-CH_2NH_2$), arylalkyl (e.g. $-CH_2Ph$ or $-CH_2-CH_2-Ph$), cyano, dialkylamino (e.g. $-N(CH_3)_2$), halo,

haloalkoxy (e.g. $-OCF_3$ or $-OCHF_2$), haloalkyl (e.g. $-CF_3$), alkyl (e.g. $-CH_3$ or $-CH_2CH_3$), -OH, -CHO, $-NO_2$, aryl (optionally substituted with alkoxy, haloalkoxy, halogen, alkyl or haloalkyl), heteroaryl (optionally substituted with alkoxy, haloalkoxy, halogen, alkyl or haloalkyl), heterocycloalkyl, aminoacyl (e.g. $-CONH_2$, $-CONHCH_3$), aminosulfonyl (e.g. $-SO_2NH_2$, $-SO_2NHCH_3$), acylamino (e.g. $-NHCOCH_3$), sulfonylamino (e.g. $-NHSO_2CH_3$), heteroarylalkyl, cyclic amine (e.g. morpholine), aryloxy, heteroaryloxy, arylalkyloxy (e.g. benzyloxy) and heteroarylalkyloxy.

Components of formula (1) may contain one or more asymmetric centres and can thus occur as racemates and racemic mixtures, single enantiomers, disastereomeric mixtures and individual disastereomers. The present invention is meant to comprehend all such isomeric forms of the compound of Formula (1).

Some of the compound described herein may contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist with different points of attachment of hydrogen, referred to as tautomers. Such an example may be a ketone and its enol form known as keto enol tautomers. The individual tautomers as well as mixtures thereof are encompassed with compounds of formula (1).

Compounds of the formula (1) may be separated into diastereoisomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventionial means, for example by the use of an optically active amine as a resolving agent or on a chiral HPLC column. Alternatively, any enantiomer of a compound of the general formula (1) may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration.

The term 'pharmaceutically acceptable salts' refers to salts prepared from pharmaceutically acceptable non–toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminium, ammonium, calcium, copper, ferric, ferrous, lithium,

magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, *N,N'*–dibenzylethylenediamine, 2–diethylaminoethanol, 2–dimethylaminoethanol, ethanolamine, ethylenediamine, N–ethylipiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methyglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from the pharmaceutically acceptable non–toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulphuric, tartaric, p–toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulphuric, and tartaric acids.

It will be understood that, as used in herein, references to the compounds of Formula (1) are meant to also include the pharmaceutically acceptable salts.

Compounds of this invention are antagonists of the MCH receptor and as such are useful for the prevention and treatment of disorders or diseases associated with the MCH receptor. Accordingly, another aspect of the present invention provides a method for the treatment (including prevention, alleviation, amelioriation or suppression) of diseases or disorders or symptoms medicated by MCH receptor binding and subsequent cell activation, which comprises administering to a mammal an effective amount of a compound of Formula (1). Such diseases, disorders, conditions or symptoms are for example, obesity, diabetes, appetite and eating disorders, cardiovascular disease, hypertension,

dyslipidemia, myocardial infarction, gall stones, osteroarthritis, certain cancers, AIDS wasting, cachexia, frailty (particularly in the elderly), binge eating disorders including bulimia, anorexia, mental disorders including manic depression, depression, schizophrenia, mood disorders, delirium, dementia, severe mental retardation, anxiety, stress, cognitive disorders, sexual function, reproductive function, kidney function, diuresis, locomotor disorders, attention deficit disorder (ADD), substance abuse disorders and dyskinesias including Parkinson's disease, Parkinson like syndromes, Tourette's syndrome, Huntington's disease, epilepsy, improving memory function, and spinal muscular atrophy.

The utilities of the present compounds in these diseases or disorders may be demonstrated in animal disease models that have been reported in the literature. The following are examples of such animal disease models: a) suppression of food intake and resultant weight loss in rats (*Life Sciences*, **1998**, 63, 113-117); b) reduction of sweet food intake in marmosets (*Behavioural Pharm*, **1998**, 9, 179-181); c) the reduction of sucrose and ethanol intake in mice (*Psychopharm.* **1997**, 132, 104 – 106); d) increased motor activity and place conditioning in rats (*Psychopharm.* **1998**, 135, 324-332; *Psychopharmacol.* **2000**, 151: 25-30); e) spontaneous locomotor activity in mice (*J. Pharm. Exp. Ther.* **1996**, 277, 586 – 594).

The magnitude of prophylactic or therapeutic dose of a compound of Formula (1) will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound of Formula (1) and its route of administration. It will also vary according to the age, weight and response of the individual patient. In general, the daily dose range lie within the range of from about 0.001 mg to about 100 mg per kg body weight of a mammal, preferably 0.01 mg to about 50 mg per kg, and most preferably 0.1 to 10 mg per kg, in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

For use where a composition for the intravenous administration is employed, a suitable dosage range is from about 0.001 mg to about 25 mg (preferably from 0.01 mg to about 1 mg) of a compound of Formula (1) per kg of body weight per day and for cytoprotective use from about 0.1mg to about 100

mg (preferably from about 1 mg to about 100 mg and more preferably from about 1mg to about 10 mg) of a compound of Formula (1) per kg of body weight per day.

In the cases where an oral composition is employed, a suitable dosage range is, e.g. from about 0.01mg to about 100mg of a compound of Formula (1) per day, preferably from about 0.1mg to about 10mg per day. For oral administration, the compositions are preferably provided in the form of tablets containing from 0.01 to 1,000mg, preferably 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 20.0, 25.0, 30.0, 40.0, 50.0 or 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated.

Another aspect of the present invention provides pharmaceutical compositions which comprise a compound of Formula (1) and a pharmaceutically acceptable carrier. The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) (pharmaceutically acceptable excipients) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of Formula (1), additional active ingredient(s), and pharmaceutically acceptable excipients.

Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dosage of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like.

The pharmaceutical compositions of the present invention comprise a compound of Formula (1) as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable

carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (aerosol inhalation), or nasal administration, although the most suitable route in any case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

For administration by inhalation, the compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulizers. The compounds may also be delivered as powders which may be formulated and the power composition may be inhaled with the aid of insufflation powder inhaler device. The preferred delivery systems for inhalation are metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of a compound of Formula (1) in suitable propellants, such as fluorocarbons or hydrocarbons and dry powder inhalation (DPI) aerosol, which can be formulated as a dry powder of a compound of Formula (1) with or without additional excipients.

Suitable topical formulations of a compound of formula (1) include transdermal devices, aerosols, creams, ointments, lotions, dusting powders and the like.

In practical use, the compounds of Formula (1) can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g. oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such, as, for example, water, glycols, oils, alcohols, flavouring agents, preservatives, colouring agents and the like in the case of oral liquid

preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, the compounds of Formula (1) may also be administered by controlled release means and/or delivery devices such as those described in U.S Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200 and 4,008,719.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 1 mg to about 500 mg of the

active ingredient and each cachet or capsule contains from about 1 to about 500 mg of the active ingredient.

The following are examples of representative pharmaceutical dosage forms for the compounds of Formula (1):

Injectable Suspension (I.M.)	**mg/mL**
Compound of Formula (1)	10
Methylcellulose	5.0
Tween 80	0.5
Benzyl alcohol	9.0
Benzalkonium chloride	1.0
Water for injection to a total volume of 1mL	

Tablet	**mg/tablet**
Compound of Formula (1)	25
Microcrystalline Cellulose	415
Povidone	14.0
Pregelatinized Starch	43.5
Magnesium Stearate	2.5
	500

Capsule	**mg/capsule**
Compond of Formula (1)	25
Lactose Powder	573.5
Magnesium Stearate	1.5
	600

Aerosol	**Per canister**
Compound of Formula (1)	24mg
Lecithin, NF Liq. Conc.	1.2mg
Trichlorofluoromethane, NF	4.025g
Dichlorodifluoromethane, NF	12.15g

Compounds of Formula (1) may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of Formula (1) are useful. Such other drugs may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with a compound of Formula (1). When a compound of Formula (1) is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of Formula (1) is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of Formula (1). It will be appreciated that for the treatment or prevention of eating disorders, including obesity, bulimia nervosa and compulsive eating disorders, a compound of the present invention may be used in conjunction with other anorectic agents.

The present invention also provides a method for the treatment or prevention of eating disorders, which method comprises administration to a patient in need of such treatment an amount of a compound of the present invention and an amount of an anorectic agent, such that together they give effective relief.

Suitable anorectic agents for use in combination with a compound of the present invention include, but are not limited to, aminorex, amphechloral, amphetamine, benzphetamine, chlorphentermine, clobenzorex, cloforex, clominorex, clortermine, cyclexedrine, dexfenfluramine, dextroamphetamine, diethylpropoin, diphemethoxidine, *N*-ethylamphetamine, fenbutrazate, fenfluramine, fenisorex, fenproporex, fludorex, fluminorex, furfurylmethylamphetamine, levamfetamine, levophacetoperane, mazindol, mefenorex, metamfepramore, methamphetamine, norpseudoephedrine, pentorex, phendimetrazine, phenmetrazine, phentermine, phenylpropanolamine, picilorex and sibutramine, and pharmaceutically acceptable salts thereof.

A particularly suitable class of anorectic agent is the halogenated amphetamine derivatives, including chorphentermine, cloforex, clortermine,

dexfenfluramine, fenfluramine, picilorex and sibutramine, and pharmaceutically acceptable salts thereof.

Particularly preferred halogenated amphetamine derivatives of use in combination with a compound of the present invention include: fenfluramine and dexfenfluramine, and pharmaceutically acceptable salts thereof.

It will be appreciated that for the treatment or prevention of obesity, the compounds of the present invention may also be used in combination with a selective serotonin reuptake inhibitor (SSRI).

The present invention also provides a method for the treatment or prevention of obesity, which method comprises administration to a patient in need of such treatment an amount of a compound of the present invention and an amount of SSRI, such that together they give effective relief.

Suitable selective serotonin reuptake inhibitors of use in combination with a compound of the present invention include fluxetine, fluvoxamine, paroxetine and sertraline, and pharmaceutically acceptable salts thereof.

The present invention also provides a method for the treatment or prevention of obesity, which method comprises administration to a patient in need of such treatment an amount of a compound of the present invention and an amount of growth hormone secretagogues such as those disclosed and specifically described in US patent 5,536,716; melanacortin agonists such as Melantan II; b-3 agonists such as those disclosed and specifically described in patent publications WO94/18161, WO95/29159, WO97/46556, WO98/04526 and WO98/32753; 5HT-2 agonists; orexin antagonists; melanin concentrating hormone antagonists; galanin antagonists; CCK agonists; GPL-1 agonists; corticotropin – releasing hormone agonists; NPY – 5 antagonists; CB1 modulators, such as N- (1 – piperidinyl) - 5 – (4 – chlorophenyl) – 1 – (2,4 – dichlorophenyl) – 4 – methylpyrazole – 3 – carboxamide (SR141716A), and those described in US Patents US 5,624,941 and US 6,028,084, PCT Application Nos. WO98/43636, WO98/31227, WO98/41519, WO98/37061, WO00/10967, WO00/10968, WO97/29079, WO99/02499 and WO08.43635, and EPO Application No. EP – 658546; WO99/02499 and WO98/43635, and EPO

Application No. EP – 658546; and Y1 antagonists, such that together they give effective relief.

As used herein "obesity" refers to a condition whereby a mammal has a body mass index (BMI), which is calculated as weight per height squared (kg/m^2), of at least 25.9. Conventionally, those persons with normal weight have a BMI of 19.9 to less than 25.9.

It will be appreciated that for treatment or prevention of obesity, the compounds of the present invention may also be used in combination with the histamine receptor – 3 (H3) modulators, CB1 cannabinoid receptor antagonists or inverse agonists, and/or phosphodiesterase – 3B (PDE3B) inhibitors.

The obesity described herein may be due to any cause, whether genetic or environmental. Examples of disorders that may result in obesity or be the cause of obesity include overeating and bulimia, polycystic ovarian disease, craniopharynagioma, the Prader–Willi Syndrome, Frohlich's syndrome, Type II diabetes, GH–deficient subjects, normal variant short stature, Turner's syndrome, and other pathological conditions showing reduced metabolic activity or a decrease in resting energy expenditure as a percentage of total fat free mass, e.g. children with acute lymphoblastic leukaemia.

"Treatment" (of obesity) refers to reducing the BMI of the mammal to less than about 25.9 and maintaining that weight for at least 6 months. The treatment suitably results in a reduction in food or calorie intake by the mammal.

"Prevention" (of obesity) refers to preventing obesity from occurring if the treatment is administered prior to the onset of the obese condition. Moreover, if treatment is commenced in already obese subjects, such treatment is expected to prevent, or to prevent the progression of, the medical sequelae of obesity, such as, e.g., arteriosclerosis, Type II diabetes, polycystic ovarian disease, cardiovascular diseases, osteoarthritis, dermatological disorders, hypertension, insulin resistance, hypercholesterolemia, hypertriglceridemia and cholelithiasis.

Excessive weight is a contributing factor to different diseases including hypertension, diabetes, dyslipidemias, cardiovascular disease, gallstones, osteoarthritis and certain forms of cancers. Bringing about weight loss can be used, for example, to reduce the likelihood of such diseases and as part of a

treatment for such diseases. Weight reduction can be achieved by antagonizing MCH–1R receptor activity to obtain, for example, one or more of the following effects: reducing appetite, increasing metabolic rate, reducing fat intake or reducing carbohydrate craving.

Other compounds that may be combined with a compound of Formula (1), either administered separately or in the same pharmaceutical compositions, for the treatment of diabetes and other sequelae or existing weight include but are not limited to:

(a) insulin sensitizers including (i) PPARg agonists such as the glitazones (e.g. troglitazone, piolitazone, englitazone, MMC-555, BRL49653 and the like), and compounds disclosed in WO97/27857, 97/38137 and 97/27847; (ii) biguanides such as metfirmin and phenformin;

(b) Insulin or insulin mimetics;

(c) Sulfonylureas, such as tolbutamide and glipizide;

(d) a - glucosidase inhibitors (such as acarbose),

(e) Cholesterol lowering agents such as (i) HMG – CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastain, and other statins), (ii) sequestrants (chloestyramine, colestipol and dialkylaminoalkl derivatives or a cross – linked dextran), (iii) nicotinyl alcohol, nicotinic acid or a salt thereof, (iv) proliferator–activator receptor a agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and benzafibrate), (v) inhibitors of cholesterol absorption for example beta–sitosterol and (acyl CoA: cholesterol acyltransferase) inhibitors for example melinamide, (vi) probucol, (vii) vitamin E, and (viii) thyromimetics;

(f) PPARd agonists, such as those disclosed in WO97/28149;

(g) Antiobesity compounds, such as fenfluramine, dexfenfluramine, phentermine, sibutramine, orlistat, or b3 adrenergic receptor agonists;

(h) Feeding behaviour modifying agents, such as neuropeptide Y antagonists (e.g. neuropeptide Y5) such as those disclosed in WO 97/19682, WO 97/20820, WO 97/20821, WO 97/20822 and WO 97/20823;

(i) PPARa agonists such as described in WO 97/36579 by Glaxo;

(j) PPARg agonists as described in WO97/10813;

(k) Serotonin reuptake inhibitors such as fluxetine and sertraline;

(l) Growth hormone secretagogues such as MK – 0677.

It will be appreciated that for the treatment or prevention of stress, a compound of the present invention may be used in conjunction with other anti–stress agents, such as anti–anxiety agents. Suitable classes of anti–anxiety agents include benzodiazepines and 5-HT_{1A} agonists or antagonists, especially 5-HT_{1A} partial agonists, and corticotropin releasing factor (CRF) antagonists.

Suitable benzodiazepines include: alprazolam, chloridazepoxide, clonazepam, chlorazepate, diazepam, halazepam, lorazepam, oxzepam and prazepam, and pharmaceutically acceptable salts thereof.

Suitable 5-HT_{1A} receptor agonists or antagonists include, in particular the 5–HT_{1A} receptor partial agonists buspirone, flesinoxan, gepirone and ipsapirone, and pharmaceutically acceptable salts thereof.

Suitable CRF antagonists include the 4-tetrahydropyridylpyrimidine derivatives disclosed in US 6,187,781; the aryloxy and arylthio–fused pyrimidine and pyrimidine derivatives disclosed in US 6,124,300; the arylamino–fused pyrimidine derivatives disclosed in US 6,107,300; the pyrazole and pyrazolopyrimidine derivatives disclosed in US 5,705,656, US 5,712,303, US 5,968,944, US 5,958,948, US 6,103,900 and US 6,005,109; the tetrahydropteridine derivatives disclosed in US 6,083,948; the benzoperimidine carboxylic acid derivatives disclosed in US 5,861,398; the substituted 4-phenylaminothiazol derivatives disclosed in US 5,880,135; the cyclic CRF analogs disclosed in US 5,493,006, US 5,663,292 and US 5,874,227; and the compounds disclosed in US 5,063,245, US 5,245,009, US 5,510,458 and US 5,109,111; as well as compounds described in International Patent Specification Nos. WO 94/13643, WO 94/13644, WO 94/13661, WO 94/13676 and WO 94/13677.

As used herein, the term "substance abuse disorder" includes substance dependence or abuse with or without physiological dependence. The substances associated with these disorders are: alcohol, amphetamines (or amphetamine-like substances), caffeine, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine (or phencyclidine-like compounds),

sedative-hypnotics or benzodiazepines, and other (or unknown) substances and combinations of all the above.

In particular, the term "substance abuse disorders" includes drug withdrawal disorders such as alcohol withdrawal with or without perceptual disturbances; alcohol withdrawal delirium; amphetamine withdrawal; cocaine withdrawal; nicotine withdrawal; opioid withdrawal; sedative, hypnotic or anxiolytic withdrawal with or without perceptual disturbances; sedative, hypnotic or anxiolytic withdrawal delirium; and withdrawal symptoms due to other substances. It will be appreciated that reference to treatment of nicotine withdrawal includes the treatment of symptoms associated with smoking cessation.

Other "substance abuse disorders" include substance-induced anxiety disorder with onset during withdrawal; substance-induced mood disorder with onset during withdrawal; and substance-induced sleep disorder with onset during withdrawal.

Similarly, compounds of Formula (1) will be useful as a partial or complete substitute for conventional pain relievers in preparations wherein they are presently co-administered with other agents or ingredients. Thus in further aspects, the invention encompasses pharmaceutical compositions for modulating the perception of pain comprising a non-toxic therapeutically effective amount of the compound of Formula (1) as defined above and one or more ingredients such as another pain reliever including acetaminophen or phenacetin, or a cyclooxygenase-2 (COX-2) inhibitor; a potentiator including caffeine; a prostaglandin including misoprostol, enprostil, rioprostil, ornoprostol or rosaprostol; a sedating or non-sedating antihistamine. Examples of cyclooxygenase-2 selective inhibitos include rofecoxib (VIOXX®, see U.S Patent No. 5,474,995), etoricoxib (ARCOXIA™ see U.S. Patent No 5,861,419), celecoxib (CELEBREX®, see U.S. Patent No. 5,466,823), valdecoxib (see U.S. No. 6,633,272), parecoxib (see U.S. No. 5,932,598), COX-189 (Novartis), BMS347070 (Bristol Myers Squibb), tiracoxib (JTE522, Japan Tobacco), ABT963 (Abbott), CS502 (Sankyo) and GW406381 (GlaxoSmithKline). Other examples of cyclooxygenase-2 inhibitors compounds are disclosed in U.S. Patent No.

6,020,343. In addition the invention encompasses a method of treating pain comprising: administration to a patient in need of such treatment a non-toxic therapeutically effective amount of the compound of Formula (1), optionally co-administered with one or more of such ingredients as listed immediately above.

Suitable antipsychotic agents of use in combination with a compound of the present invention for the treatment of schizophrenia include the phenothiazine, thioxanthene, heterocyclic dibenzazepine, butyrophenone, diphenylbutylpiperidine and indolone classes of antipsychotic agent. Suitable examples of phenothiazines include chlorpromazine, mesoridazine, thioridazine, aceophenazine, fluphenazine, perphenazine and trifluoperazine. Suitable examples of thioxanthenes include chlorprothixene and thiothixene. Suitable examples of dibenzazepines include clozapine and olanzapine. An example of a butyrophenone is haloperidol. An example of a diphenylbutylpiperidine is pimozide. An example of an indolone is molindolone. Other antipsychotic agents includ loxapine, sulphiride and risperidone. It will be appreciated that the antipsychotic agents whn used in combination with a CB1 receptor modulator may be in the form of a pharmaceutically acceptable salt, for example, chlorpromazine hydrochloride, mesoridazine besylate, thioridazine, hydrochloride, acetophenazine maleate, fluphenazine hydrochloride, flurphenazine enathate, fluphenazine decanoate, trifluoperazine hydrochloride, thiothixene hydrochloride, haloperidol decanoate, loxapine succinate and molindone hydrochloride. Perhenazine, chlorprothixene, clozapine, olanzapine, haloperidol, pimozide and risperidone are commonly used in a non-salt form.

Other classes of antipsychotic agent of use in combination with a compound of the present invention include dopamine receptor antagonists, especially D2, D3 and D4 dopamine receptor antagonists, and muscarinic M1 receptor agonists. An example of a D3 dopamine receptor antagonist is the compound PNU-99194A. An example of a D4 dopamine receptor antagonist is PNU-101387. An example of a muscarinic M1 receptor agonist is xanomeline.

Another class of antipsychotic agent of use in combination with CB1 receptor modulator is the 5-HT_{2A} receptor antagonists, examples of which include MDL100907 and fananserin. Also of use in combination with a compound of the

present invention are the serotonin dopamine antagonists (SDAs) which are believed to combine 5-HT_{2A} and dopamine receptor antagonist activity, examples of which include olanzapine and ziperasidone.

It will be appreciated that for the treatment of depression or anxiety, a compound of the present invention may be used in conjunction with other anti-depressant or anti-anxiety agents.

Suitable classes of anti-depressant agents include norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotrophin releasing factor (CRF) antagonists, α-adrenoreceptor antagonists, neurokinin-1 antagonists and atypical anti-depressants.

Suitable norepinephrine reuptake inhibitors include tertiary amine tricyclics and secondary amine tricyclics. Suitable examples of tertiary amine tricyclics include: amitriptyline, clomipramine, doxepin, imipramine and trimipramine, and pharmaceutically acceptable salts thereof. Suitable examples of secondary amine tricyclics include: amoxapine, desipramine, maprotiline, nortriptyline and protripyline, and pharmaceutically acceptable salts thereof.

Suitable selective serotonin reuptake inhibitors include those described *supra*.

Suitable monoamine oxidase inhibitors include: isocarboxazid, phenelzine, tranylcypromine and selediline, and pharmaceutically acceptable salts thereof.

Suitable reversible inhibitors of monoamine oxidase include: moclobemide, and pharmaceutically acceptable salts thereof.

Suitable serotonin and noradrenaline reuptake inhibitors of use in the present invention include: venlafaxine, and pharmaceutically acceptable salts thereof.

Suitable CRF antagonists include those described hereinabove

Suitable atypical anti-depressants include: bupropion, lithium, nefazodone, trazodone and viloxazine, and pharmaceutically acceptable salts thereof.

The neurokinin-1 receptor antagonist may be peptidal or non-peptidal in nature, however, the use of a non-peptidal neurokinin-1 receptor antagonist is preferred. In a preferred embodiment, the neurokinin-1 receptor antagonist is a CNS-penetrant neurokinin-1 receptor antagonist. In addition, for convenience the use of an orally active neurokinin-1 receptor antagonist is preferred. To facilitate dosing, it is also preferred that the neurokinin-1 receptor antagonist is a long acting neurokinin-1 receptor antagonist. An especially preferred class of neurokinin-1 receptor antagonist of use in the present invention are those compounds which are orally active and long acting.

Neurokinin-1 receptor antagonists of use in the present invention are fully described, for example, in U.S. Patent Nos. 5,162,339, 5,232,929, 5,242,930, 5,373,003, 5,387,595, 5,459,270, 5,494,926, 5,496,833, 5,637,699; European Patent Publication Nos. EP0 360 390, 0 394 989, 0 428 434, 0 429 366, 0 430 771, 0 436 334, 0 443 132, 0 482 539, 0 498 069, 0 499 313, 0 512 901, 0 512 902, 0 514 273, 0 514 274, 0 514 275, 0 514 276, 0 515 681, 0 517 589, 0 520 555, 0 522 808, 0 528 495, 0 532 456, 0 553 280, 0 536 817, 0 545 478, 0 558 156, 0 577 394, 0 585 913, 0 590 152, 0 599 538, 0 610 793, 0 634 404, 0 686 629, 0 693 489, 0 694 535, 0 699 655, 0 699 674, 0 707 006, 0 708 101, 0 709 375, 0 709 376, 0 714 891, 0 723 959, 0 733 632 and 0 776 893; PCT International Patent Publication Nos. WO 90/05525, 90/05729, 91/09844, 91/18899, 92/01688, 92/06079, 92/12151, 92/15585, 92/17449, 92/20661, 92/20676, 92/21677, 92/22569, 93/00330, 93/00331, 93/01159, 93/01165, 93/01169, 93/01170, 93/06099, 93/09116, 93/10073, 93/14084, 93/14113, 93/18023, 93/19064, 93/21155, 93/21181, 93/23380, 93/24465, 94/00440, 94/01402, 94/02461, 94/02595, 94/03429, 94/03445, 94/04494, 94/04496, 94/05625, 94/07843, 94/08997, 94/10165, 94/10167, 94/10168, 94/10170, 94/11368, 94/13639, 94/13663, 94/14767, 94/15903, 94/19320, 94/19323, 94/20500, 94/26735, 94/26740, 94/29309, 95/02595, 95/04040, 95/04042, 95/06645, 95/07886, 95/07908, 95/08549, 95/11880, 95/14017, 95/15311, 95/16679, 95/17382, 95/18124, 95/18129, 95/19344, 95/20575, 95/21819, 95/22525, 95/23798, 95/26338, 95/28418, 95/30674, 95/30687, 95/33744, 96/05181, 9605193, 96/05203, 96/06094, 96/07649, 96/10562, 96/16939,

96/18643, 96/20197, 96/21661, 96/29304, 96/29317, 96/29326, 96/29328, 96/31214, 96/32385, 96/37489, 97/01553, 97/01554, 97/03066, 97/08144, 97/14671, 97/17362, 97/18206, 97/19084, 97/19942, 97/21702, and 97/49710; and in British Patent Publication Nos. 2 266 529, 2 268 931, 2 269 170, 2 269 590, 2 271 774, 2 294 144, 2 293 168, 2 293 169, and 2 302 689.

Suitable classes of anti-anxiety agents include benzodiazepines and 5-HT_{1A} agonists or antagonists, especially 5-HT_{1A} partial agonists, and corticotropin releasing factor (CRF) antagonists.

Suitable benzodiazepines include those previously described herein.

Suitable 5-HT_{1A} receptor agonists or antagonists include, in particular, those described *supra*.

For the treatment of autism, the compounds of the present invention may be used in combination with butyrophenones.

For the treatment of Parkinson's disease and Parkinson-like syndromes, the compounds of the present invention may be used in combination with levodopa, carbidopa/levodopa, amantadine, bromocryptine and other ergot alkaloids, anticholinergic medications such as benztrophine, trihexyphenidyl, antihistamines such as dephenhydramine and orphenadrine, mild sedatives, tricyclic antidepressants such as amitriptiline and others described *supra*, and propanolol.

For the treatment of Huntingdon's Chorea, the compounds of the present invention may be used in combination with phenothiazine, chlorpromazine, and butyrophenone neuroleptics such as haloperidol or reserpine.

For the treatment of epilepsy, the compounds of the present invention may be used together with anticonvulsants such as penytoin, phenobarbital, primidone, carbamazepine, trimethadione, clonazepam, valproate and ethosuximide.

In one embodiment of a combination for the treatment of male or female sexual dysfunctions, the second ingredient to be combined with a compound of Formula (1) can be type V cyclic-GMP-specific phosphodiesterase (PDE-V) inhibitor, such as sildenafil and IC-351 or a pharmaceutical acceptable salt thereof; an alpha-adrenergic receptor antagonist, such as phentolamine and

yohimbine or a pharmaceutically acceptable salt therefore; or a dopamine receptor agonist, such as apomorphine or a pharmaceutically acceptable salt thereof.

"Male sexual dysfunction" includes impotence, loss of libido, and erectile dysfunction. "Erectile dysfunction" is a disorder involving the failure of a male mammal to achieve erection, ejaculation, or both. Symptoms of erectile dysfunction include an inability to achieve or maintain an erection, ejactulatory failure, premature ejaculation, or inability to achieve an orgasm. An increase in erectile dysfunction and sexual dysfunction can have numerous underlying causes, including but not limited to (1) ageing, (2) and underlying physical dysfunction, such as trauma, surgery and peripheral vascular disease, and (3) side-effects resulting from drug treatment, depression, and other CNS disorders. "Female sexual dysfunction" can be seen as resulting from multiple components including dysfunction in desire, sexual arousal, sexual receptivity, and orgasm related to disturbances in the clitoris, vagina, periurethral glans, and other trigger points of sexual function. In particular, anatomic and functional modification of such trigger points may diminish the orgasmic potential in breast cancer and gynecologic cancer patients. Treatment of female sexual dysfunction with a MC-4 receptor agonist can result in improved blood flow, improved lubrication, improved sensation, facilitation of reaching orgasm, reduction in the refractory period between orgasms, and improvements in arousal and desire. In a broader sense, "female sexual dysfunction" also incorporates sexual pain, premature labor, and dysmenorrhea.

For the treatment of male and female sexual dysfunction, the compounds of the present invention may be employed in combination with a compound selected from a type V cyclic-GMP-specific phosphodiesterase (PDE-V) inhibitor, such as sildenafil and IC-351 or a pharmaceutically acceptable salt thereof; an alpha-adrenergic receptor antagonist, a such as phentolamine and yohimbine or a pharmaceutically acceptable salt thereof; or a dopamine receptor agonist, such as apomophine or a pharmaceutically acceptable salt thereof.

MCH-1R antagonist compounds can be provided in kit. Such a kit typically contains as active compound in dosage forms for administration. A

dosage form contains a sufficient amount of active compound such that a beneficial effect can be obtained when administered to a patient during regular intervals, such as 1 to 6 times a day, during the course of 1 or more days. Preferable, a kit contains instructions indicating the use of the dosage form for weight reduction (e.g., to treat obesity or overweight) or stress reduction, and the amount of dosage form to be taken over a specified time period.

The method of treatment of this invention comprises a method of treating melanin concentrating hormone receptor mediated diseases by administering to a patient in need of such treatment a non-toxic therapeutically effective amount of a compound of this invention that selectively antagonizes the MCH receptor in preference to the other G-protein coupled receptors. In particular, the present invention comprises a method of treating MCR-1R receptor subtype mediated diseases by administering a patient in need of such treatment a non-toxic therapeutically effective amount of a compound of this invention that selectively antagonizes the MCH-1R receptor.

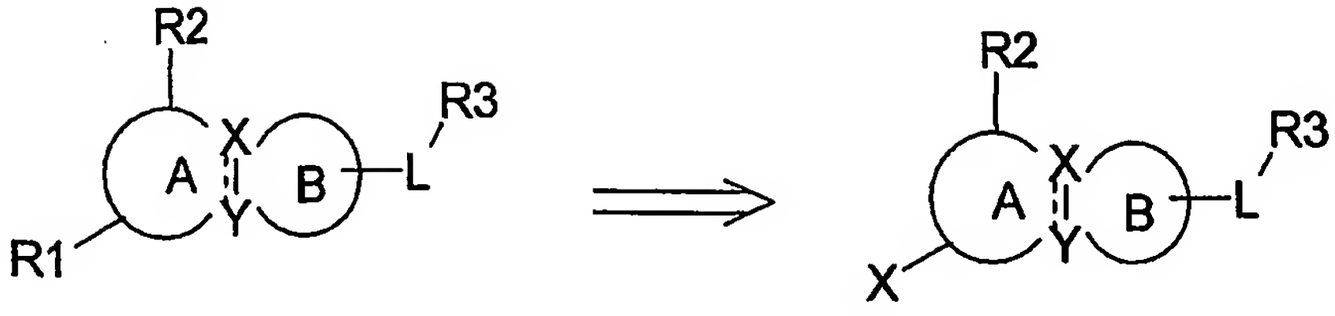
The weight ratio of the compound of the Formula (1) to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the Formula (1) is combined with a β-3 agonist the weight ratio of the compound of the Formula (1) to the β-3 agonist will generally range from about 1000:1 to about 1:1000, preferable about 200:1 to about 1:200. Combinations of a compound of the Formula (1) and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

The compounds of Formula (1) of the present invention can be prepared according to the procedures of the following Schemes and Examples, using appropriate materials and are further exemplified by the following specific examples. Moreover, by utilizing the procedures described with the disclosure contained herein, one of ordinary skill in the art can readily prepare additional compounds of the present invention claimed herein. The compounds illustrated in the examples are not, however, to be construed as forming the only genus that is considered as the invention. The Examples further illustrate details for the

preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. The instant compounds may be isolated in the form of their pharmaceutically acceptable salts, such as those described previously herein above. The free amine bases corresponding to the isolated salts can be generated by neutralization with a suitable base, such as aqueous sodium hydrogen carbonate, sodium carbonate, sodium hydroxide, and potassium hydroxide, and extraction of the liberated amine free base into an organic solvent followed by evaporation. The amine free base isolated in this manner can be further converted into another pharmaceutically acceptable salt by dissolution in an organic solvent followed by addition of the appropriate acid and subsequent evaporation, precipitation, or crystallization.

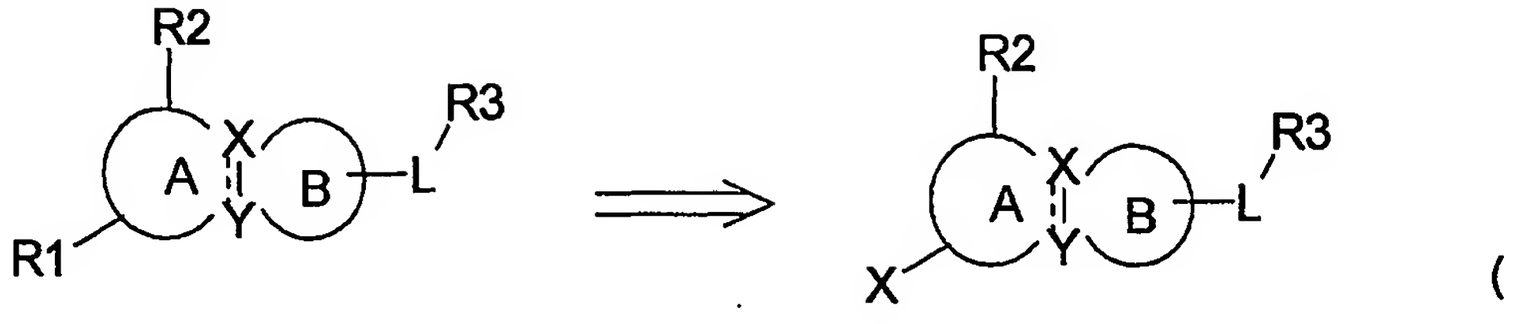
It may be necessary to protect reactive functional groups (e.g. hydroxy, amino, thio or carboxy) in intermediates used in the preparation of compounds of formula (1) to avoid their unwanted participation in a reaction leading to the formation of compounds of formula (1). Conventional protecting groups, for example those described by T. W. Greene and P. G. M. Wuts in "Protective groups in organic chemistry" John Wiley and Sons, 1999, may be used. In the reaction schemes provided below, all definitions of R1 to R12 are to be understood to include such protected functional groups.

Compounds of formula (1) in which R1 represents NR4R5 may be prepared from compounds of formula (2) (in which X represents a halogen) by treatment of a compound of formula (2) with the appropriate amine HNR4R5. The reaction may be carried out using any standard conditions known to those skilled in the art, such as using an excess of the amine, either neat or in the presence of a suitable solvent, at elevated temperature. Suitable solvents include alcoholic solvents, and hydrocarbon solvents, such as toluene.



(1) (2)

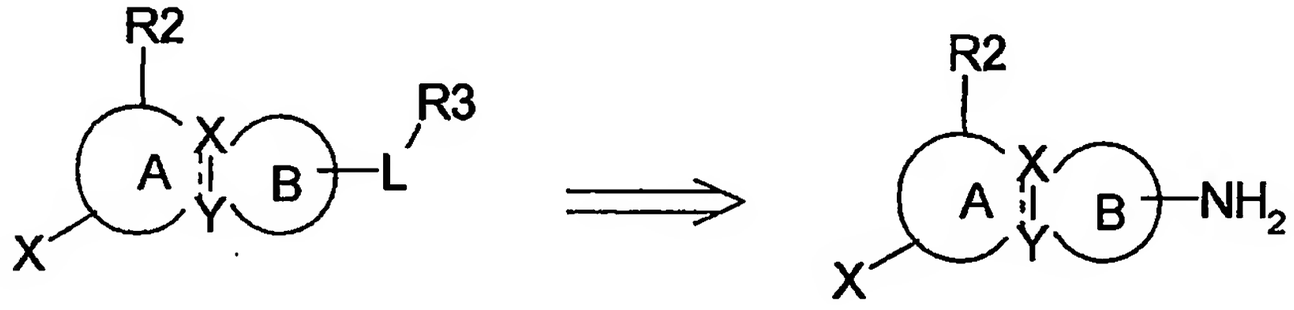
Compounds of formula (1) in which R1 represents optionally substituted aryl, heteroaryl, aryl-fused-cycloalkyl, heteroaryl-fused-cycloalkyl, aryl-fused-heterocycloalkyl or heteroaryl-fused-heterocycloalkyl may be conveniently prepared from compounds of formula (2) (in which X represents chlorine, bromine or iodine) by using a metal-mediated coupling reaction with an appropriate aryl or heteroaryl derivative. For example, a halocompound may be reacted with an aryl or heteroaryl boronic acid or boronate ester in the presence of a palladium catalyst such as [1,1-*bis*(diphenylphosphino) ferrocene]dichloropalladium (II) and in the presence of a suitable base, such as cesium carbonate, in a suitable solvent, such as 1,4-dioxane, at an appropriate temperature, such as elevated temperature. It may be advantageous to conduct the reaction in a microwave. Alternatively, a halocompound may be reacted with an appropriate tin compound, for example a tri-n-butylstannyl analogue, in the presence of a palladium catalyst, such as dichloro*bis*-(triphenylphosphine) palladium and triphenylphosphine, in an appropriate solvent, such as xylene, at a suitable temperature, such as the reflux temperature of the solvent. It will be appreciated by those skilled in the art there are many ways to form a bond between the central ring system and an aryl or heteroaryl group. A list of examples of biaryl bond forming reactions which could be used is provided by Fu et *al. J. Am. Chem. Soc.* **2001**, 123, 2719-2724 and by Lemaire *et al. Chem. Rev.* **2002**, 102, 1359-1469.



(1) (2)

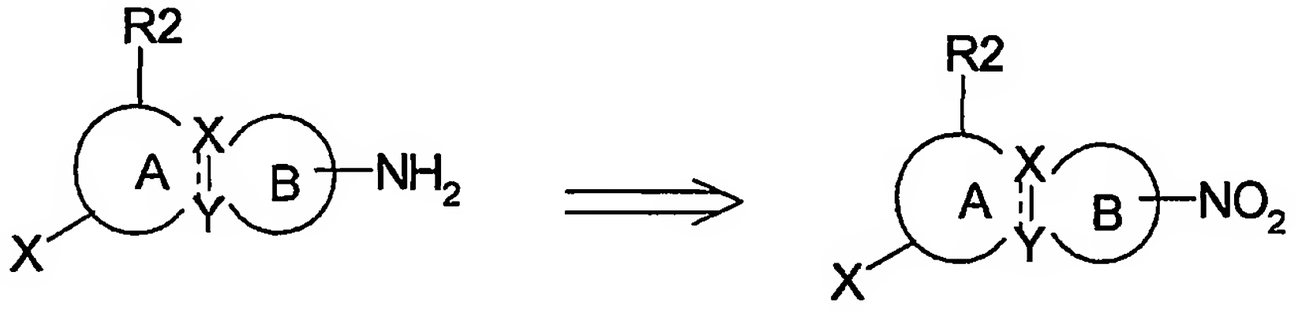
Compounds of formula (2) in which L represents $-(CH_2)_nN(R11)CO(CH_2)_m-$, $(CH_2)_nN(R11)SO_2(CH_2)_m-$, $-(CH_2)_nN(R11)CO(CH_2)_mO(CH_2)_p-$, $-(CH_2)_nN(R11)SO_2(CH_2)_mO(CH_2)_p-$, $-(CH_2)_nN(R11)CO(CH_2)_mS(CH_2)_p-$, $-(CH_2)_nN(R11)SO_2(CH_2)_mS(CH_2)_p-$, $-(CH_2)_nN(R11)CO(CH_2)_mN(R11)(CH_2)_p-$, $-(CH_2)_nN(R11)SO_2(CH_2)_mN(R11)(CH_2)_p-$, or $-(CH_2)_nN(R11)(CH_2)_m-$ and n represents 0 can be readily prepared from an aminocompound of formula (3). Compounds of formula (2) in which L contains an amide can be obtained by reaction of an aminocompound of formula (3) with an appropriate carboxylic acid using any suitable standard conditions known to those skilled in the art. For example, the reaction can be conducted using an activating agent such as *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate in the presence of a base such as *N,N*-diisopropylamine in a suitable solvent such as dichloromethane, dimethylformamide, or a mixture of the two. Alternatively, the carboxylic acid may be converted into a reactive intermediate such as an acid chloride or mixed anhydride and this can be reacted with the aminocompound (3) in the presence of a suitable base, such as triethylamine, in a suitable solvent, such as dichloromethane. The reactive intermediate may be used in situ without isolation, or it may be isolated and then treated with the aminocompound (3). Similarly, compounds of formula (2) in which L contains a sulphonamide may be prepared by reaction of an aminocompound of formula (3) with a sulphonyl chloride in the presence of a suitable base, such as triethylamine, in a suitable solvent, such as dichloromethane. Compounds of formula (2) in which L contains a urea may be prepared by reaction of an aminocompound of formula (3) with an appropriate isocyanate in the presence of a suitable base, such as

triethylamine, in a suitable solvent, such as dichloromethane. Compounds of formula (2) in which L contains an -N(R11)(CH_2)- group can be prepared from aminocompounds of formula (3) an appropriate aldehyde under reactive amination conditions. Suitable conditions include the use of a reducing agent, such as triacetoxyborohydride, in a suitable solvent such as 1,2-dichloroethane.



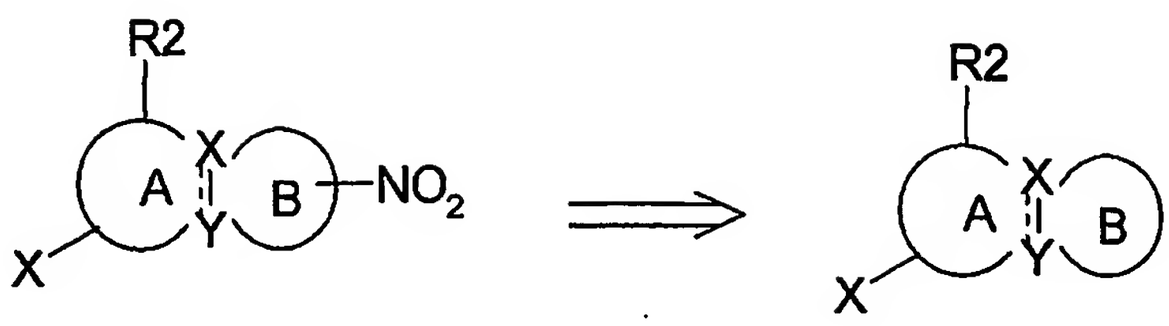
(2) (3)

Aminocompounds of formula (3) can be prepared by reduction of nitrocompounds of formula (4). The reduction may be carried out using any suitable conditions known to those skilled in the art, for example by using a metal such as iron or tin in the presence of an acid, such as hydrochloric acid, in a suitable solvent, such as ethanol, at an appropriate temperature, such as the reflux temperature of the solvent.



(3) (4)

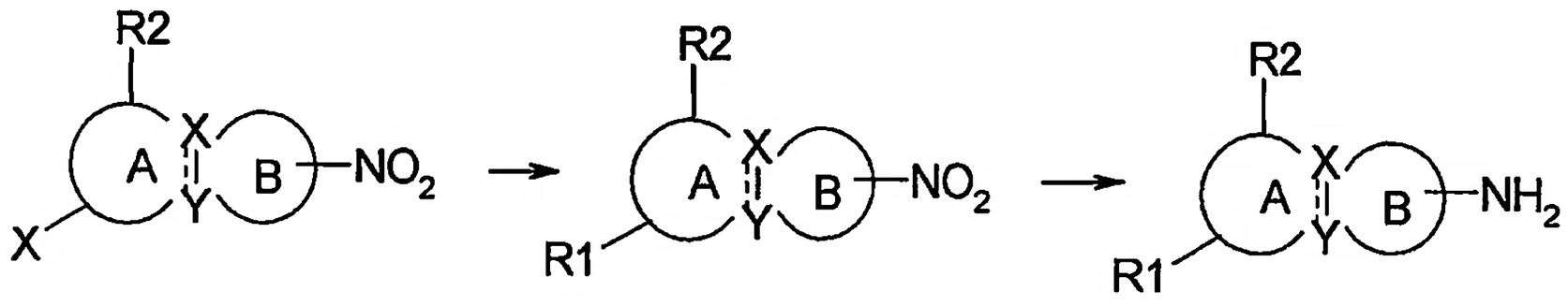
Nitrocompounds of formula (4) can be obtained from compounds of formula (5) by nitration, which can be carried out using any suitable conditions such as the use of fuming nitric acid and concentrated sulphuric acid at reduced temperature.



(4) (5)

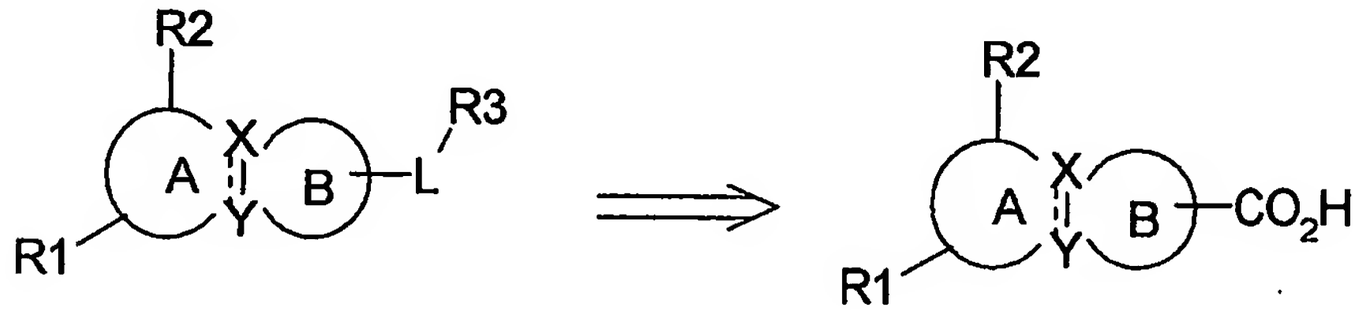
Compounds of formula (5) may be prepared using any standard methods known to those skilled in the art, or may be commercially available. Standard methods for the formation of heterocycles are described in standard texts such as Advances in Heterocyclic Chemistry (Ed. Katritzky), The Chemistry of Heterocyclic Compounds (Ed. Weissberger and Taylor), Comprehensive Heterocyclic Chemistry (Pub. Pergamon Press), Comprehensive Heterocyclic Chemistry II (Pub. Pergamon Press) and Heterocyclic Compounds (Ed. Jones, Pub. Wiley). Some specific examples of methods for the preparation of appropriate heterocycles are provided herein by way of example.

It will be appreciated by those skilled in the art that the reactions described above may be conducted in a different order. For example, a nitrocompound of formula (4) may be converted into a nitrocompound of formula (6) using either an appropriate amination reaction, or an appropriate metal catalysed biaryl bond formation as discussed previously in relation to the preparation of a compound of formula (1) from a compound of formula (2). Subsequent reduction of the nitrocompound of formula (6) would provide an aminocompound of formula (7), which could then be converted into a compound of formula (1).



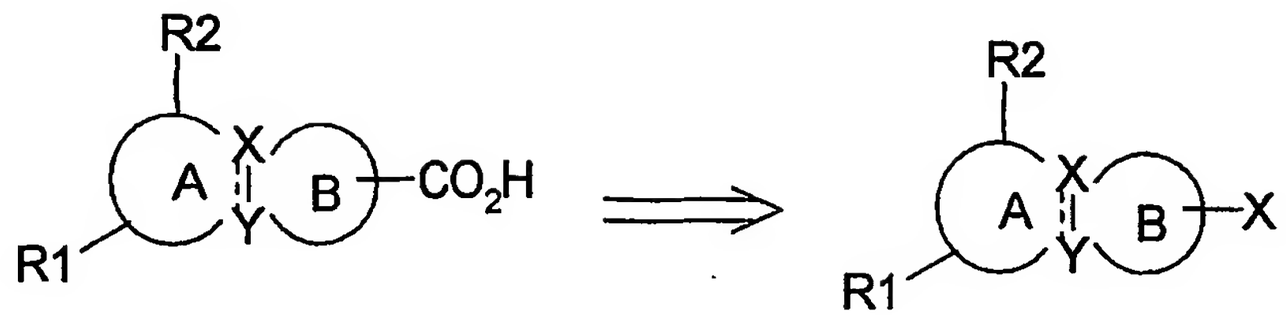
(4) (6) (7)

Compounds of formula (1) in which L represents $-(CH_2)_nCON(R11)(CH_2)_m-$, $-(CH_2)_nCON(R11)(CH_2)_rO-$, $-(CH_2)_nCON(R11)(CH_2)_rS-$ or $-(CH_2)_nCON(R11)(CH_2)_rN(R11)-$ in which n represents 0 could be prepared from a carboxylic acid of formula (8) by reaction with an appropriate amine using any suitable standard conditions known to those skilled in the art. For example, the reaction can be conducted using an activating agent such as *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate in the presence of a base such as *N,N*-diisopropylamine in a suitable solvent such as dichloromethane, dimethylformamide, or a mixture of the two. Alternatively, the carboxylic acid may be converted into a reactive intermediate such as an acid chloride or mixed anhydride and this can be reacted with the amine in the presence of a suitable base, such as triethylamine, in a suitable solvent, such as dichloromethane. The reactive intermediate may be used *in situ* without isolation, or it may be isolated and then treated with the amine.



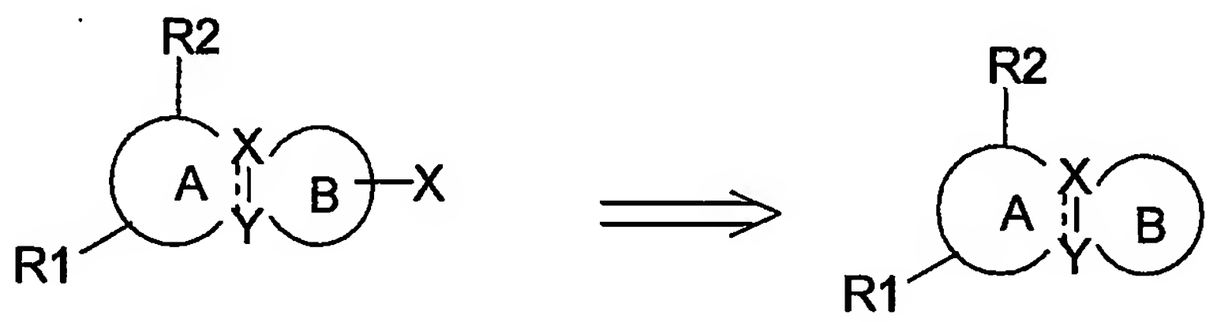
(1) (8)

A carboxylic acid of formula (8) may be prepared from a halocompound of formula (9) (in which X represents chlorine, bromine or iodine) using a metal catalysed carbonylation reaction, such as a palladium catalysed reaction. The carbonylation reaction can be carried out using carbon monoxide in the presence of a suitable catalyst, such as bis(triphenylphosphine) palladium chloride and a suitable base, such as triethylamine in appropriate solvent(s), such as methanol and water. The reaction may be carried out at any appropriate temperature and pressure, such as a temperature of 110°C and a pressure of 10 bar.



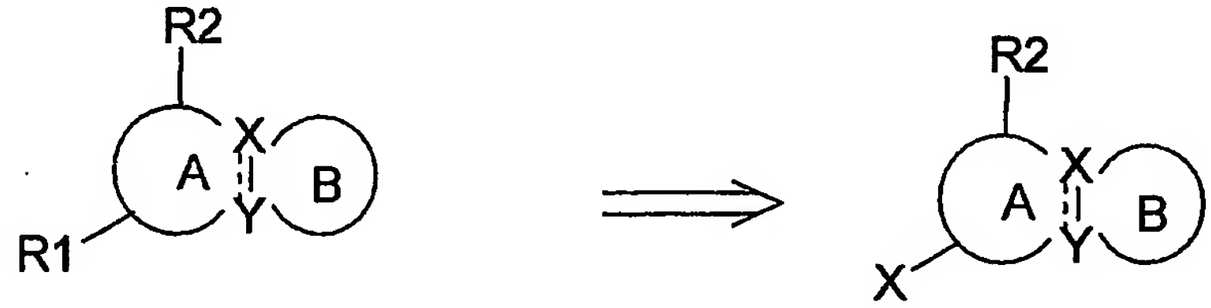
(8) (9)

A halocompound of formula (9) may be prepared from a compound of (10) using standard conditions for aromatic halogenation. For example, a compound of formula (10) may be treated with a halogenating agent such as chlorine, N-chlorosuccinimide, bromine, N-bromosuccinimide, N-iodosuccinimide or iodine in a suitable solvent, such as dichloromethane.



(9) (10)

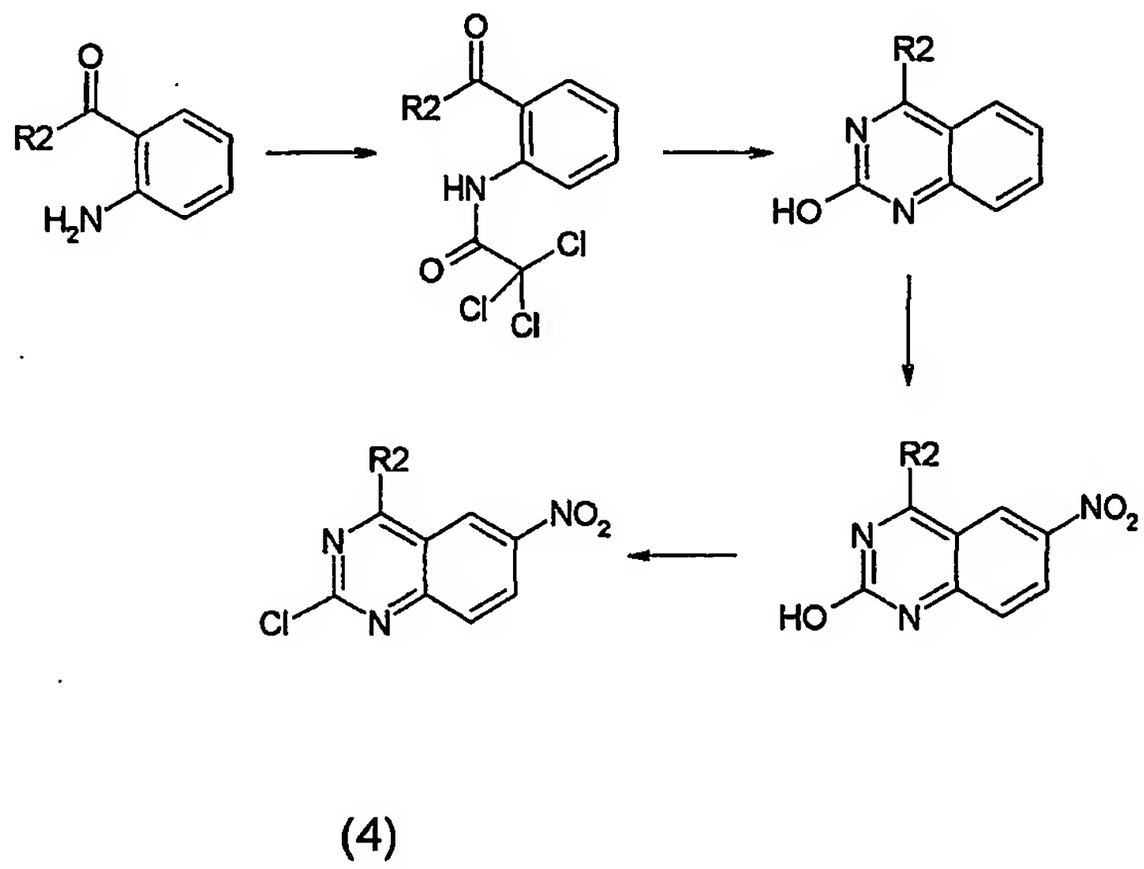
A compound of formula (10) may be prepared from a compound of formula (5) using any suitable method, such as those described earlier.



(10) (5)

A suitable method for the preparation of a compound of formula (4) (in which X represents chlorine) in which the ring system is a quinazoline is shown below. Reaction of an appropriate aminoketone with trichloroacetyl chloride can be carried out in the presence of a suitable base, such as 4-

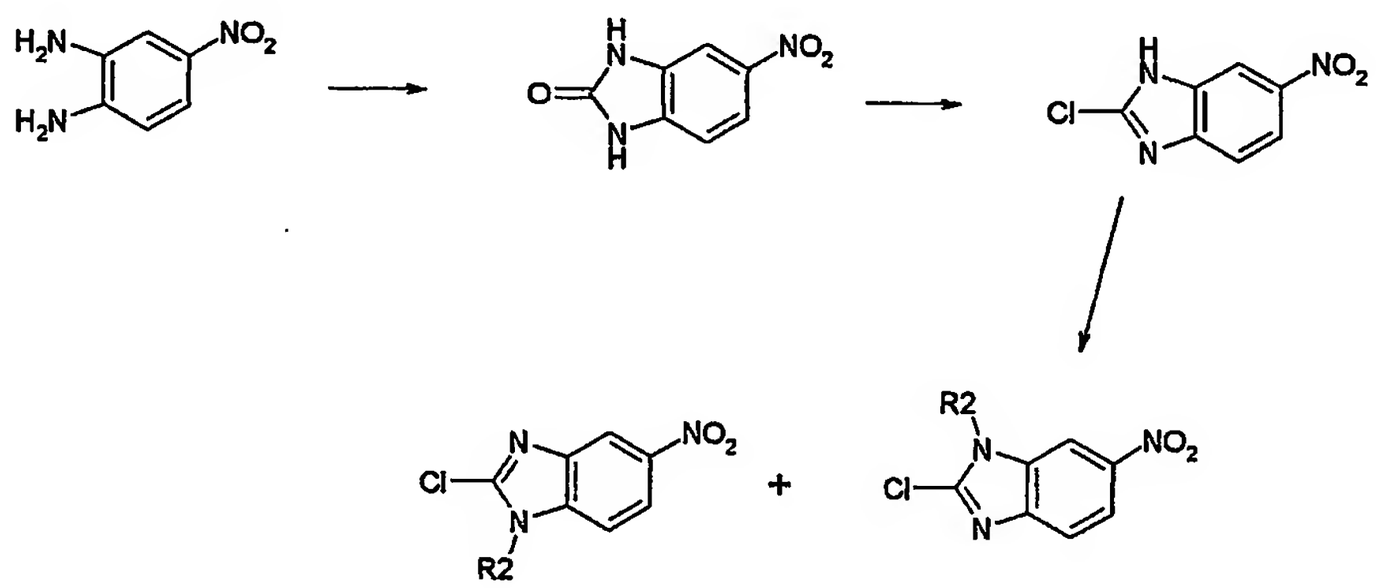
dimethylaminopyridine, in a suitable solvent, such as tetrahydrofuran, at an appropriate temperature, such as 0°C. Cyclisation can be achieved using any suitable conditions known to those skilled in the art, for example using ammonium acetate in a suitable solvent, such as dimethylsulphoxide. Nitration can be carried out using concentrated nitric acid and concentrated sulphuric acid at a suitable temperature, such as 0°C. Compounds of formula (4) can then be obtained using any suitable chlorination conditions, for example by using phosphorus oxychloride at a suitable temperature, such as an elevated temperature.



(4)

A suitable method for the preparation of a compound of formula (4) (in which X represents chlorine) in which the ring system is a benzimidazole is shown below. 1,2-Diamino-4-nitrobenzene can be converted into a benzimidazole using any suitable method known to those skilled in the art. For example, 1,2-diamino-4-nitrobenzene can be treated with urea in a suitable solvent, such as *N,N*-dimethylformamide at an appropriate temperature, such as the reflux temperature of the solvent. The resultant dihydrobenzimidazol-2-one can be converted into the corresponding 2-chlorobenzimidazole using any appropriate chlorination conditions, such as by using phosphorus oxychloride at an appropriate temperature, such as an elevated temperature. Subsequent conversion to a compound of formula (4) can be achieved using any appropriate

conditions known to those skilled in the art. For example, compounds of formula (4) in which R2 represents alkyl or alkyl-R6 may be obtained using appropriate alkylation conditions, for example by using a suitable alkylating reagent R2-X (in which X represents a halogen) in the presence of a suitable base, such as sodium hydride, in a suitable solvent, such as *N,N*-dimethylformamide, at an appropriate temperature, such as 0°C. It will be appreciated by those skilled in the art that such an alkylation reaction may result in the formation of a mixture of regioisomers, which can be separated at any suitable stage during the synthesis.



(4)

Compounds of formula (1) – (10) may be prepared using any suitable procedures known to those skilled in the art, including appropriate functional group inter-conversion. It will be appreciated that such functional group inter-conversions may be carried out at any suitable stage during the synthesis.

For example primary amine (-NH_2) groups may be alkylated using a reductive alkylation process employing an aldehyde or a ketone and a borohydride, for example sodium triacetoxyborohydride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, for example 1,2-dichloroethane, or an alcohol such as ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature. Secondary amine (-NH-) groups may be similarly alkylated employing an aldehyde.

In a further example, primary amine or secondary amine groups may be converted into amide groups (-NHCOR' or -NRCOR') by acylation. Acylation may be achieved by reaction with an appropriate acid chloride in the presence of a base, such as triethylamine, in a suitable solvent, such as dichloromethane, or by reaction with an appropriate carboxylic acid in the presence of a suitable coupling agent such HATU (*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate) in a suitable solvent such as dichloromethane. Similarly, amine groups may be converted into sulphonamide groups ($-NHSO_2R'$ or $-NR''SO_2R'$) groups by reaction with an appropriate sulphonyl chloride in the presence of a suitable base, such as triethylamine, in a suitable solvent such as dichloromethane. Primary or secondary amine groups can be converted into urea groups (-NHCONR'R" or -NRCONR'R") by reaction with an appropriate isocyanate in the presence of a suitable base such as triethylamine, in a suitable solvent, such as dichloromethane.

An amine ($-NH_2$) may be obtained by reduction of a nitro ($-NO_2$) group, for example by catalytic hydrogenation, using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethyl acetate or an alcohol e.g. methanol. Alternatively, the transformation may be carried out by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

In a further example, amine ($-CH_2NH_2$) groups may be obtained by reduction of nitriles (-CN), for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon, or Raney nickel, in a solvent such as an ether e.g. a cyclic ether such as tetrahydrofuran, at a temperature from –78°C to the reflux temperature of the solvent.

In a further example, amine ($-NH_2$) groups may be obtained from carboxylic acid groups ($-CO_2H$) by conversion to the corresponding acyl azide ($-CON_3$), Curtius rearrangement and hydrolysis of the resultant isocyanate (-N=C=O).

Aldehyde groups (-CHO) may be converted to amine groups ($-CH_2NR'R''$)) by reductive amination employing an amine and a borohydride, for example

sodium triacetoxyborohydride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, for example dichloromethane, or an alcohol such as ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature.

In a further example, aldehyde groups may be converted into alkenyl groups (-CH=CHR') by the use of a Wittig or Wadsworth-Emmons reaction using an appropriate phosphorane or phosphonate under standard conditions known to those skilled in the art.

Aldehyde groups may be obtained by reduction of ester groups (such as -CO_2Et) or nitriles (-CN) using diisobutylaluminium hydride in a suitable solvent such as toluene. Alternatively, aldehyde groups may be obtained by the oxidation of alcohol groups using any suitable oxidising agent known to those skilled in the art.

Ester groups (-CO_2R') may be converted into the corresponding acid group (-CO_2H) by acid- or base-catalused hydrolysis, depending on the nature of R. If R is t-butyl, acid-catalysed hydrolysis can be achieved for example by treatment with an organic acid such as trifluoroacetic acid in an aqueous solvent, or by treatment with an inorganic acid such as hydrochloric acid in an aqueous solvent.

Carboxylic acid groups (-CO_2H) may be converted into amides (-CONHR' or -CONR'R") by reaction with an appropriate amine in the presence of a suitable coupling agent, such as HATU, in a suitable solvent such as dichloromethane.

In a further example, carboxylic acids may be homologated by one carbon (i.e -CO_2H to -CH_2CO_2H) by conversion to the corresponding acid chloride (-COCl) followed by Arndt-Eistert synthesis.

In a further example, -OH groups may be generated from the corresponding ester (e.g. -CO_2R'), or aldehyde (-CHO) by reduction, using for example a complex metal hydride such as lithium aluminium hydride in diethyl ether or tetrahydrofuran, or sodium borohydride in a solvent such as methanol. Alternatively, an alcohol may be prepared by reduction of the corresponding acid (-CO_2H), using for example lithium aluminium hydride in a solvent such as tetrahydrofuran, or by using borane in a solvent such as tetrahydrofuran.

Alcohol groups may be converted into leaving groups, such as halogen atoms or sulfonyloxy groups such as an alkylsulfonyloxy, e.g. trifluoromethylsulfonyloxy or arylsulfonyloxy, e.g. p-toluenesulfonyloxy group using conditions known to those skilled in the art. For example, an alcohol may be reacted with thionyl chloride in a halogenated hydrocarbon (e.g. dichloromethane) to yield the corresponding chloride. A base (e.g. triethylamine) may also be used in the reaction.

In another example, alcohol or phenol groups may be converted to ether groups by coupling a phenol with an alcohol in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl, or dimethylazodicarboxylate. Alternatively ether groups may be prepared by deprotonation of an alcohol, using a suitable base e.g. sodium hydride followed by subsequent addition of an alkylating agent, such as an alkyl halide.

Aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange by treatment with a base, for example a lithium base such as nbutyl or tbutyl lithium, optionally at a low temperature, e.g. around –78°C, in a solvent such as tetrahydrofuran, and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using N,N-dimethylformamide as the electrophile. Aromatic halogen substituents may alternatively be subjected to metal (e.g. palladium or copper) catalysed reactions, to introduce, for example, acid, ester, cyano, amide, aryl, heteraryl, alkenyl, alkynyl, thio- or amino substituents. Suitable procedures which may be employed include those described by Heck, Suzuki, Stille, Buchwald or Hartwig.

Aromatic halogen substituents may also undergo nucleophilic displacement following reaction with an appropriate nucleophile such as an amine or an alcohol. Advantageously, such a reaction may be carried out at elevated temperature in the presence of microwave irradiation.

As another example, compounds of formula (1) in which R1 is heteroaryl containing an N-oxide group (e.g. pyridine-N-oxide) may be prepared by

oxidation of compounds of formula (1) in which R1 is the corresponding non-oxidised heteroaryl.

It will be appreciated by those skilled in the art that the functional group interconversions described above may be carried out at any suitable stage of the synthesis.

The following Examples are provided solely to illustrate the present invention and are not intended to limit the scope of the invention, as described herein.

^{1}H NMR spectra were recorded at ambient temperature using a Varian Unity Inova (400MHz) spectrometer with a triple resonance 5mm probe. Chemical shifts are expressed in ppm relative to tetramethylsilane. The following abbreviations have been used: br = broad signal, s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet.

High Pressure Liquid Chromatography - Mass Spectrometry (LCMS) experiments to determine retention times (R_T) and associated mass ions were performed using one of the following methods.

Method A: Experiments performed on a Micromass Platform LCT spectrometer with positive ion electrospray and single wavelength UV 254nm detection using a Higgins Clipeus C18 5mm 100 x 3.0mm column and a 2 ml/minute flow rate. The initial solvent system was 95% water containing 0.1% formic acid (solvent A) and 5% acetonitrile containing 0.1% formic acid (solvent B) for the first minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 14 minutes. The final solvent system was held constant for a further 2 minutes.

Method B: Experiments performed on a Micromass Platform LC spectrometer with positive and negative ion electrospray and ELS/Diode array detection using a Phenomenex Luna C18(2) 30 x 4.6mm column and a 2 ml/minute flow rate. The solvent system was 95% solvent A and 5% solvent B for the first 0.50 minutes followed by a gradient up to 5% solvent A and 95% solvent B over the next 4 minutes. The final solvent system was held constant for a further 0.50 minutes.

Microwave experiments were carried out using a Personal Chemistry Smith Synthesizer™, which uses a single-mode resonator and dynamic field tuning, both of which give reproducibility and control. Temperatures from 40-250°C can be achieved, and pressures of up to 20bar can be reached. Two types of vial are available for this processor, 0.5-2.0ml and 2.0-5.0ml.

Intermediate 1

2-(Trichloroacetylamino)acetophenone

Trichloroacetyl chloride (1.63g) was added slowly to a stirred, cooled mixture of 2-aminoacetophenone (1.21g) and 4-dimethylaminopyridine (1.09g) in tetrahydrofuran while maintaining the temperature at 0°C. The mixture was allowed to warm to room temperature and was stirred for 2h. It was evaporated to dryness and the residue was purified by chromatography on silica eluting with a mixture of pentane and dichloromethane (1:1) to give 2-(trichloroacetylamino)acetophenone (2.34g).

^{1}H NMR (DMSO-d_6) d 12.9 (br s, 1H) 8.4 (d, 1H) 8.2 (d, 1H) 7.75 (t, 1H) 7.4 (t, 1H) 2.7 (s, 3H)

Intermediate 2

4-Methylquinazolin-2-one

Ammonium acetate (2.6g) was added to a solution of 2-(trichloroacetyl-amino)acetophenone (intermediate 1, 1.89g) in dimethylsulphoxide. The mixture was stirred for 24h until a solid precipitated. Water was added and the resultant solid was collected by filtration and air dried to give 4-methylquinazolin-2-one as a white solid (0.7g).

LCMS (method B) retention time 1.70 min, ($M+H^+$) 161

Intermediate 3

4-Methyl-6-nitroquinazolin-2-one

Concentrated nitric acid (1.5ml) was added to a stirred, cooled solution of 4-methylquinazolin-2-one (intermediate 2, 0.39g) in concentrated sulphuric acid (10ml) while maintaining the temperature below 5°C. The mixture was

stirred at 0°C for 1h then poured onto crushed ice. The resultant mixture was basified by addition of aqueous sodium hydroxide solution (5M) and the precipitate was collected by filtration and air dried to give 4-methyl-6-nitroquinazolin-2-one as a red solid (0.48g).

LCMS (method B) retention time 2.02 min, $(M+H^+)$ 206

Intermediate 4

2-Chloro-4-methyl-6-nitroquinazoline

A mixture of 4-methyl-6-nitroquinazolin-2-one (intermediate 3, 0.48g) and phosphorus oxychloride (10ml) was stirred and heated at reflux for 2h. The cooled mixture was poured onto a mixture of ice and water. It was extracted with ethyl acetate, washed with water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness to give 2-chloro-4-methyl-6-nitroquinazoline (0.14g).

^1H NMR ($CDCl_3$) d 9.1 (d, 1H) 8.7 (dd, 1H) 8.1 (d, 1H) 3.1 (s, 3H)

Intermediate 5

4-Methyl-2-(1-pyrrolidino)-6-nitroquinazoline

Pyrrolidine (130ml) was added to a solution of 2-chloro-4-methyl-6-nitroquinazoline (intermediate 4, 115mg) in toluene and the resultant mixture was stirred and heated at reflux for 20h. The cooled mixture was evaporated to dryness and the residue was purified by chromatography on silica eluting with a mixture of dichloromethane and methanol (19:1) to give 4-methyl-2-(1-pyrrolidino)-6-nitroquinazoline (125mg).

^1H NMR (DMSO-d_6) d 8.8 (d, 1H) 8.35 (dd, 1H) 7.55 (d, 1H) 3.6 (m, 4H) 2.85 (s, 3H) 1.95 (m, 4H)

By proceeding in a similar manner the following intermediate was prepared from the appropriate starting materials:

Intermediate 6

2-[N-(2-Dimethylaminoethyl)-N-methylamino]-4-methyl-6-nitroquinazoline

^1H NMR (DMSO-d_6) d 8.8 (d, 1H) 8.4 (dd, 1H) 7.5 (d, 1H) 3.9 (m, 2H) 3.2 (br s, 2H) 2.85 (s, 3H) 2.2 (s, 6H)

From intermediate 4 and *N,N,N'*-trimethylethylenediamine

Intermediate 7

6-Amino-4-methyl-2-(1-pyrrolidino)quinazoline

4-Methyl-2-(1-pyrrolidino)-6-nitroquinazoline (intermediate 5, 110mg) was added to a solution of stannous chloride (380mg) in concentrated hydrochloric acid (1ml). The mixture was stirred at room temperature for 15minutes then heated at 100°C for 2h. The cooled solution was poured into ice and basified by addition of aqueous sodium hydroxide solution (5M). The resultant mixture was extracted with ethyl acetate, washed with water, dried ($MgSO_4$), filtered and the filtrate was evaporated to dryness. The residue was triturated with diethyl ether and pentane to give 6-amino-4-methyl-2-(1-pyrrolidino)quinazoline as a brown solid (35mg).

^{1}H NMR (DMSO-d_6) d 7.3 (d, 1H) 7.1 (dd, 1H) 6.8 (d, 1H) 5.1 (br s, 1H) 3.5 (m, 4H) 2.6 (s, 3H) 1.9 (m, 4H)

By proceeding in a similar manner the following intermediate was prepared from the appropriate starting material:

Intermediate 8

6-Amino 2-[N-(2-dimethylaminoethyl)-N-methylamino]-4-methylquinazoline

^{1}H NMR (DMSO-d_6) d 7.25 (d, 1H) 7.1 (dd, 1H) 6.9 (d, 1H) 5.15 (br s, 2H) 3.75 (t, 2H) 3.1 (s, 3H) 2.6 (s, 3H) 2.4 (t, 2H) 2.2 (s, 6H)

From intermediate 6

Intermediate 9

6-Amino-2-(3-furyl)-4-methylquinazoline

A mixture of 2-chloro-4-methyl-6-nitroquinazoline (intermediate 4, 100mg), 3-furanboronic acid (75mg), [1,1-bis(diphenylphosphino) ferrocene]dichloropalladium (II), complex with dichloromethane (1:1) (74mg) and aqueous cesium carbonate solution (2M, 0.7ml) in dimethylformamide was degassed and purged with nitrogen then heated in the microwave at 130°C for 30 minutes. The mixture was diluted with ethyl acetate and filtered through celite. The filtrate was washed with water, dried ($MgSO_4$) and filtered. The filtrate was

evaporated to dryness to give 6-amino-2-(3-furyl)-4-methylquinazoline as a brown oil (74mg).

LCMS (method B) retention time 2.4 min, $(M+H^+)$ 226

Intermediate 10

5-Nitro-1,3-dihydrobenzimidazol-2-one

A solution of 1,2-diamino-4-nitrobenzene (3.0g) and urea (7.06g) in dimethylformamide was stirred and heated at reflux for 5h. The cooled mixture was poured into water and the solid was collected by filtration. The solid was suspended in hot water and the remaining solid was collected. The resultant solid was then suspended in hydrochloric acid (1M), stirred and the remaining solid was collected and air dried to give 5-nitro-1,3-dihydrobenzimidazol-2-one as a tan coloured solid (1.9g).

^{1}H NMR (DMSO-d_6) d 11.4 (br s, 1H) 11.2 (br s 1H) 7.95 (dd, 1H) 7.7 (d, 1H) 7.1 (d, 1H)

Intermediate 11

2-Chloro-5-nitrobenzimidazole

Concentrated hydrochloric acid (5 drops) was added to a suspension of 5-nitro-1,3-dihydrobenzimidazol-2-one (intermediate 10, 0.96g) in phosphorus oxychloride (25ml) and the mixture was stirred and heated at reflux for 7h. The cooled mixture was poured into a mixture of ice and water and the precipitated product was extracted into ethyl acetate. The organic phase was dried ($MgSO_4$), filtered and the filtrate was evaporated to give 2-chloro-5-nitrobenzimidazole as a tan coloured solid (0.9g).

^{1}H NMR (DMSO-d_6) d 14.0 (br s, 1H) 8.45 (br s, 1H) 8.15 (d, 1H) 7.7 (d, 1H)

Intermediates 12 & 13

2-Chloro-1-methyl-6-nitro-1H-benzimidazole and 2-chloro-1-methyl-5-nitro-1H-benzimidazole

Sodium hydride (60% oil dispersion, 201mg) was added to a stirred, cooled solution of 2-chloro-5-nitrobenzimidazole (intermediate 11, 900mg) in dimethylformamide while maintaining the temperature at 0°C. The mixture was then stirred at room temperature for 2h. Iodomethane (648mg) was added and the mixture was stirred at room temperature for 3h. The mixture was poured into water and the precipitated solid was collected by filtration and air dried to give a mixture of 2-chloro-1-methyl-6-nitro-1H-benzimidazole and 2-chloro-1-methyl-5-nitro-1H-benzimidazole as a tan-coloured solid (840mg).

^{1}H NMR (DMSO-d_6) d 8.7 (d, 1H) 8.5 (d, 1H) 8.25 (dd, 1H) 8.15 (dd, 1H) 7.9 (d, 1H) 7.8 (d, 1H) 3.95 (s, 3H) 3.9 (s, 3H)

Intermediates 14 & 15

6-Amino-2-chloro-1-methyl-1H-benzimidazole and 5-amino-2-chloro-1-methyl-1H-benzimidazole

The mixture of 2-chloro-1-methyl-6-nitro-1H-benzimidazole and 2-chloro-1-methyl-5-nitro-1H-benzimidazole (intermediates 12 & 13, 400mg) was added to a stirred solution of stannous chloride (1.26g) in concentrated hydrochloric acid (10ml). The resultant mixture was stirred for 15 minutes then heated at 100°C for 3h. After cooling the mixture was poured into a mixture of ice and water and basified to pH 9 by addition of aqueous sodium hydroxide solution (3M). The mixture was evaporated to dryness and the residue was extracted into a mixture of acetonitrile and chloroform (1:1). The solution was evaporated to dryness to give a mixture of 5-amino-2-chloro-1-methyl-1H-benzimidazole and 6-amino-2-chloro-1-methyl-1H-benzimidazole as a pink solid (320mg).

^{1}H NMR (DMSO-d_6) d 7.2 (d, 2H) 6.7 (s, 1H) 6.65 (d, 1H) 6.55 (s, 1H) 6.5 (d, 1H) 5.1 (br s, 2H) 4.85 (br s, 2H) 3.7 (s, 3H) 3.6 (s, 3H)

In a separate experiment the two isomers were separated by chromatography on silica eluting with dichloromethane then increasing amounts of acetonitrile to a ratio of dichloromethane to acetonitrile of 7:3.

The faster running component was isolated as 6-amino-2-chloro-1-methyl-1H-benzimidazole (intermediate 14).

^{1}H NMR (DMSO-d_6) d 7.2 (d, 1H) 6.55 (s, 1H) 6.5 (d, 1H) 5.1 (br s, 2H) 3.6 (s, 3H)

The slower running component was isolated as 5-amino-2-chloro-1-methyl-1H-benzimidazole (intermediate 15).

^{1}H NMR (DMSO-d_6) d 7.2 (d, 1H) 6.7 (s, 1H) 6.65 (d, 1H) 4.85 (br s, 2H) 3.7 (s, 3H)

By proceeding in a similar manner the following compound was prepared from the appropriate intermediate:

Intermediate 16

5-Amino-2-chlorobenzimidazole

^{1}H NMR (DMSO-d_6) d 7.1 (d, 1H) 6.6 (s, 1H) 6.45 (d, 1H) 4.8 (br s, 2H)

From intermediate 11

Intermediates 17 & 18

N-(2-Chloro-1-methyl-1H-benzimidazol-6-yl) 2-trifluoromethylphenoxy)acetamide and N-(2-Chloro-1-methyl-1H-benzimidazol-5-yl) 2-trifluoromethylphenoxy)-acetamide

A mixture of 6-amino-2-chloro-1-methyl-1H-benzimidazole and 5-amino-2-chloro-1-methyl-1H-benzimidazole (intermediates 14 & 15, 150mg), 4-trifluoromethylphenoxyacetic acid (200mg), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (410mg) and *N,N*-diisopropylethyalamine (432ml) in dichloromethane and dimethylformamide (1:1) was stirred for 4h and allowed to stand overnight. The mixture was partitioned between dichloromethane and water. The organic phase was washed with water, dried ($MgSO_4$), filtered and the filtrate was evaporated to dryness. The residue was purified by chromatography on silica eluting with dichloromethane to give a mixture of N-(2-chloro-1-methyl-1H-benzimidazol-6-yl) 2-trifluoromethylphenoxy)acetamide and N-(2-chloro-1-methyl-1H-benzimidazol-5-yl) 2-trifluoromethylphenoxy)acetamide as a red solid (300mg).

^{1}H NMR (DMSO-d_6) d 10.6 (br s, 1H) 10.4 (br s, 1H) 8.05 (s, 1H) 7.95 (s, 1H) 7.7 (d, 4H) 7.55 (m, 3H) 7.35 (d, 1H) 7.2 (d, 4H) 4.9 (s, 2H) 4.85 (s, 2H) 3.8 (s, 3H) 3.75 (s, 3H)

By proceeding in a similar manner the following compounds were prepared from the appropriate starting materials:

Intermediate 17

N-(2-Chloro-1-methyl-1H-benzimidazol-6-yl) 2-(4-trifluoromethylphenoxy)acetamide

^{1}H NMR (DMSO-d_6) d 10.6 (br s, 1H) 8.05 (s, 1H) 7.7 (d, 2H) 7.55 (d, 1H) 7.35 (d, 1H) 7.2 (d, 2H) 4.85 (s, 2H) 3.8 (s, 3H)

From intermediate 14 and 4-trifluoromethylphenoxyacetic acid

Intermediate 18

N-(2-Chloro-1-methyl-1H-benzimidazol-5-yl) 2-trifluoromethylphenoxy)acetamide

^{1}H NMR (DMSO-d_6) d 10.6 (br s, 1H) 8.0 (s, 1H) 7.7 (d, 2H) 7.55 (m, 2H) 7.2 (d, 2H) 4.85 (s, 2H) 3.75 (s, 3H)

From intermediate 15 and 4-trifluoromethylphenoxyacetic acid

Intermediate 19

N-(2-Chlorobenzimidazol-5-yl) 2-(4-trifluoromethylphenoxy)acetamide

^{1}H NMR (DMSO-d_6) d 10.4 (br s, 1H) 8.0 (s, 1H) 7.7 (d, 2H) 7.5 (d, 1H) 7.35 (d, 1H) 7.2 (d, 2H) 4.85 (s, 2H)

From intermediate 16 and 4-trifluoromethylphenoxyacetic acid

Intermediate 20

4-Methyl-5-nitro-2-(1-pyrrolidinyl)pyridine

Pyrrolidine (835ml) was added to a solution of 2-chloro-4-methyl-5-nitropyridine (0.86g) in dichloromethane and the resultant mixture was stirred at room temperature overnight. Further pyrrolidine (400ml) was added and the mixture was stirred for 2h. The mixture was diluted with dichloromethane and

washed with water, dried ($MgSO_4$), filtered and the filtrate was evaporated to dryness to give 4-methyl-5-nitro-2-(1-pyrrolidinyl)pyridine as a tan-coloured solid (0.99g).

^{1}H NMR ($CDCl_3$) d 9.0 (s, 1H) 6.1 (s, 1H) 3.55 (br s, 4H) 2.6 (s, 3H) 2.05 (br s, 4H)

By proceeding in a similar manner the following compound was prepared from the appropriate starting materials:

Intermediate 21

2-[N-(2-Dimethylaminoethyl)-N-methylamino]-4-methyl-5-nitropyridine

^{1}H NMR ($CDCl_3$) d 9.0 (s, 1H) 6.25 (s, 1H) 3.75 (t, 2H) 3.15 (s, 3H) 2.6 (s, 3H) 2.5 (t, 2H) 2.3 (s, 6H)

From 2-chloro-4-methyl-5-nitropyridine and *N,N,N'*-trimethylethylenediamine

Intermediate 22

5-Amino-4-methyl-2-(1-pyrrolidinyl)pyridine

Palladium on carbon (10%, 0.1g) was added to a suspension of 4-methyl-5-nitro-2-(1-pyrrolidinyl)pyridine (intermediate 20, 0.99g) in ethanol. The mixture was hydrogenated under a balloon of hydrogen overnight. The mixture was filtered through celite and the filtrate was evaporated to dryness to give 5-amino-4-methyl-2-(1-pyrrolidinyl)pyridine as a dark brown solid (0.87g).

^{1}H NMR (DMSO-d_6) d 7.5 (s, 1H) 6.15 (s, 1H) 4.1 (br s, 2H) 3.25 (m, 4H) 2.05 (s, 3H) 1.9 (m, 4H).

By proceeding in a similar manner the following compound was prepared from the appropriate starting material:

Intermediate 23

5-Amino-2-[N-(2-dimethylaminoethyl)-N-methylamino]-4-methylpyridine

^{1}H NMR ($CDCl_3$) d 7.7 (s, 1H) 6.3 (s, 1H) 3.55 (t, 2H) 3.0 (s, 3H) 2.45 (t, 2H) 2.3 (s, 6H) 2.15 (s, 3H)

From intermediate 21

Intermediate 24

2-Amino-7-methyl-5-(1-pyrrolidinyl)thiazolo[5,4-b]pyridine

Potassium thiocyanate (0.8g) was added to a solution of 5-amino-4-methyl-2-(1-pyrrolidino)pyridine (intermediate 22, 0.18g) in glacial acetic acid and the resultant mixture was stirred and cooled to below 10°C. A solution of bromine (155ml) in acetic acid was added slowly so as to maintain the temperature below 10°C. The mixture was allowed to warm to room temperature and stirred for 2h. It was diluted with water and basified by treatment with aqueous sodium hydroxide solution (3M). The precipitated solid was removed by filtration and washed with aqueous sodium hydroxide solution (1M) and ethyl acetate. The two phases in the filtrate were separated and the aqueous phase was further extracted with ethyl acetate. The combined organic phases were washed with water, dried ($MgSO_4$), filtered and the filtrate was evaporated to dryness. The residue was purified by chromatography on silica eluting with a mixture of dichloromethane and methanol (99:1 increasing gradually to 19:1) to give 2-amino-7-methyl-5-(1-pyrrolidinyl)thiazolo[5,4-b]pyridine as an off-white solid (27mg).

^{1}H NMR (DMSO-d_6) d 7.1 (s, 2H) 6.2 (s, 1H) 3.35 (m, 4H) 2.35 (s, 3H) 1.9 (m, 4H).

By proceeding in a similar manner the following compound was prepared from the appropriate starting material:

Intermediate 25

2-Amino-5-[N-(2-dimethylaminoethyl)-N-methylamino]-7-methylthiazolo[5,4-b]pyridine

^{1}H NMR (DMSO-d_6) d 7.2 (s, 2H) 6.35 (s, 1H) 3.55 (t, 2H) 2.95 (s, 3H) 2.4 (t, 2H) 2.3 (s, 3H) 2.15 (s, 6H)

From Intermediate 23

Example 1

N-[4-Methyl-2-(1-pyrrolidino)quinazolin-6-yl] 2-(4-trifluoromethylphenoxy)acetamide

6-Amino-4-methyl-2-(1-pyrrolidino)quinazoline (intermediate 7, 69mg) was added to a mixture of 4-trifluoromethylphenoxyacetic acid (132.1mg), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (197mg) and *N,N*-diisopropylethylamine (130ml) in dimethylformamide and the resultant mixture was stirred at room temperature overnight. The mixture was evaporated to dryness and the residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The organic phase was dried ($MgSO_4$), filtered and the filtrate was evaporated to dryness. The residue was purified by chromatography on silica eluting with a mixture of dichloromethane and methanol (19:1) to give N-[4-methyl-2-(1-pyrrolidino)quinazolin-6-yl] 2-(4-trifluoromethylphenoxy)acetamide as a pale yellow solid (57mg).

LCMS (method A) retention time 6.74 min, ($M+H^+$) 431

^{1}H NMR (DMSO-d_6) d 10.6 (br s, 1H) 8.3 (d, 1H) 7.85 (dd, 1H) 7.7 (d, 2H) 7.45 d, 1H) 7.2 (d, 2H) 4.85 (s, 2H) 3.55 (m, 4H) 2.7 (s, 3H) 1.9 (m, 4H)

By proceeding in a similar manner the following compounds were prepared from the appropriate starting materials:

Example 2

N-[4-Methyl-2-(1-pyrrolidino)quinazolin-6-yl] 2-(4-chlorophenoxy)acetamide

LCMS (method A) retention time 6.24 min, ($M+H^+$) 397

^{1}H NMR (DMSO-d_6) d 10.4 (br s, 1H) 8.3 (d, 1H) 7.85 (dd, 1H) 7.45 (d, 1H) 7.35 (d, 2H) 7.05 (d, 2H) 4.85 (s, 2H) 3,55 (br s, 4H) 2.7 (s, 3H) 1.9 (m, 4H)

From intermediate 7 and 4-chlorophenoxyacetic acid

Example 3

N-{2-[N-(2-Dimethylaminoethyl)-N-methylamino]-4-methylquinazolin-6-yl} 2-(4-trifluoromethylphenoxy)acetamide

LCMS (method A) retention time 5.53 min, ($M+H^+$) 462

^1H NMR (CD_3OD) d 8.4 (d, 1H) 7.85 (dd, 1H) 7.65 (d, 2H) 7.55 (d, 1H) 7.2 (d, 2H) 4.8 (s, 2H) 4.05 (t, 2H) 3.3 (s, 3H) 3.2 (m, 2H) 2.8 (s, 9H)

From intermediate 8 and 4-trifluoromethylphenoxyacetamide

Example 4

N-[4-Methyl-2-(1-pyrrolidino)quinazolin-6-yl] 2-(4-methoxyphenoxy)acetamide

LCMS (Method A) retention time 5.65 min, ($M+H^+$) 393

^1H NMR (DMSO-d_6) d 10.3 (br s, 1H) 8.3 (d, 1H) 7.85 (dd, 1H) 7.45 (d, 1H) 7.0 (d, 2H) 6.9 (d, 2H) 5.65 (s, 2H) 3.7 (s, 3H) 3.55 (br s, 4H) 2.7 (s, 3H) 1.95 m, 4H)

From intermediate 7 and 4-methoxyphenoxyacetamide

Example 5

N-[4-Methyl-2-(1-pyrrolidino)quinazolin-6-yl] 2-(2-chlorophenoxy)acetamide

LCMS (method A) retention time 6.05 min, ($M+H^+$) 397

^1H NMR (DMSO-d_6) d 10.6 (br s, 1H) 8.3 (d, 1H) 7.8 (dd, 1H) 7.45 (d, 2H) 7.3 (m, 1H) 7.1 (dd, 1H) 7.0 (m, 1H) 4.85 (s, 2H) 3,55 (br s, 4H) 2.7 (s, 3H) 1.9 (m, 4H)

From intermediate 7 and 2-chlorophenoxyacetic acid.

Example 6

N-[2-(3-furyl)-4-methylquinazolin-6-yl] 2-(4-trifluoromethylphenoxy) acetamide

LCMS (method A) retention time 10.54 min, ($M+H^+$) 428

^1H NMR (DMSO-d_6) d 10.5 (br s 1H) 8.6 (d, 1H) 8.45 (s, 1H) 8.1 (dd, 1H) 7.95 (d, 1H) 7.8 (s, 1H) 7.7 (d, 2H) 7.2 (d, 2H) 7.1 (s, 1H) 4.95 (s, 2H) 2.5 (s, 3H)

From intermediate 9 and 4-trifluoromethylphenoxyacetamide

Example 7

N-[1-Methyl-2-(1-pyrrolidino)-1H-benzimidazol-6-yl] 2-(4-trifluoromethylphenoxy)-acetamide and N-[1-methyl-2-(1-pyrrolidino)-1H-benzimidazol-5-yl] 2-(4-trifluoromethylphenoxy)acetamide

A mixture of N-(2-chloro-1-methyl-1H-benzimidazol-6-yl) 2-(4-trifluoromethylphenoxy)acetamide and N-(2-chloro-1-methyl-1H-benzimidazol-5-yl) 2-(4-trifluoromethylphenoxy)acetamide (intermediates 17 & 18, 300mg), pyrrolidine (1.04ml) and N-methylpyrrolidin-2-one (4ml) was heated in the microwave at 180°C for 20 minutes. The mixture was evaporated to dryness and the residue was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The organic phase was washed with water, dried ($MgSO_4$), filtered and the filtrate was evaporated to dryness. The residue was purified by chromatography on silica eluting with dichloromethane then increasing amounts of methanol to a ratio of dichloromethane and methanol 49:1 to give a mixture of N-[1-methyl-2-(1-pyrrolidino)-1H-benzimidazol-6-yl] 2-(4-trifluoromethylphenoxy)acetamide and N-[1-methyl-2-(1-pyrrolidino)-1H-benzimidazol-5-yl] 2-(4-trifluoromethylphenoxy)acetamide as an off-white solid (80mg).

LCMS (method A) retention time 7.36 min, $(M+H^+)$ 419

^1H NMR (DMSO-d_6) d 10.05 (br s 1H) 9.95 (br s, 1H) 7.7 (m, 5H) 7.55 (s, 1H) 7.2 (m, 7H) 7.1 (s, 1H) 4.85 (s, 2H) 4.8 (s, 2H) 3.65 (s, 3H) 3.6 (s, 3H) 3.55 (m, 8H) 1.9 (m, 8H)

By proceeding in a similar manner the following compounds were prepared from the appropriate starting materials:

Example 8

N-[1-Methyl-2-(1-pyrrolidino)-1H-benzimidazol-6-yl] 2-(4-trifluoromethylphenoxy)-acetamide

LCMS (method A) retention time 6.01 min, $(M+H^+)$ 419

^{1}H NMR (DMSO-d_6) d 10.1 (br s, 1H) 7.7 (m, 3H) 7.2 (m, 3H) 7.1 (dd, 1H) 4.8 (s, 2H) 3.6 (s, 3H) 3.55 (t, 4H) 1.9 (m, 4H)

From intermediate 17 and pyrrolidine

Example 9

N-[1-Methyl-2-(1-pyrrolidino)-1H-benzimidazol-5-yl] 2-(4-trifluoromethylphenoxy)-acetamide

LCMS (method A) retention time 6.01 min, ($M+H^+$) 419

^{1}H NMR (DMSO-d_6) d 9.95 (br s, 1H) 7.7 (d, 2H) 7.55 (s, 1H) 7.2 (m, 5H) 4.8 (s, 2H) 3.65 (s, 3H) 3.55 (t, 4H) 1.9 (m, 4H)

From intermediate 18 and pyrrolidine

Example 10

N-[2-(1-Pyrrolidino)benzimidazol-5-yl] 2-(4-trifluoromethylphenoxy)acetamide

LCMS (method A) retention time 5.82 min, ($M+H^+$) 405

^{1}H NMR (DMSO-d_6) d 11.1 (br s, 1H) 9.95 (br s, 0.5H) 9.85 (br s, 0.5H) 7.7 (d, 2H) 7.65 (br s, 0.5H) 7.45 (br s, 0.5H) 7.2 (d, 2H) 7.05 (d, 2H) 4.8 (s, 2H) 3.4 (m, 4H) 1.95 (m, 4H)

From intermediate 19 and pyrrolidine

Example 11

N-{2-[N-(2-Dimethylaminoethyl)-N-methylamino]-1-methyl-1H-benzimidazol-6-yl} 2-(4-trifluoromethylphenoxy)acetamide

LCMS (method A) retention time 4.61 min, ($M+H^+$) 450

^{1}H NMR (DMSO-d_6) d 10.1 (br s, 1H) 7.75 (s, 1H) 7.7 (d, 2H) 7.3 (d, 1H) 7.2 (d, 2H) 7.15 (d, 1H) 4.8 (s, 2H) 3.55 (s, 3H) 3.3 (m, 2H) 2.95 (s, 3H) 2.55 (m, 2H) 2.2 (s, 6H)

From intermediate 17 and *N,N,N'*-trimethylethylenediamine

Example 12

N-{2-[N-(2-Dimethylaminoethyl)-N-methylamino]-1-methyl-1H-benzimidazol-5-yl} 2-(4-trifluoromethylphenoxy)acetamide

LCMS (Method A) retention time 5.30 min, ($M+H^+$) 450

^1H NMR (DMSO-d_6) d 10.0 (br s, 1H) 7.7 (d, 2H) 7.65 (s, 1H) 7.25 (d, 1H) 7.2 (m, 3H) 4.8 (s,2H) 3.6 (s, 3H) 3.35 (m, 2H) 2.95 (s, 3H) 2.5 (m, 2H) 2.15 (s, 6H)

From intermediate 18 and *N,N,N'*-trimethylethylenediamine

Example 13

N-[2-(4-Methylpiperazino)-1-methyl-1H-benzimidazol-6-yl] 2-(4-trifluoromethyl-phenoxy)acetamide

LCMS (method A) retention time 5.49 min, ($M+H^+$) 448

^1H NMR (DMSO-d_6) d 10.2 (br s, 1H) 7.8 (s, 1H) 7.7 (d, 2H) 7.35 (d, 1H) 7.2 (m, 3H) 4.85 (s, 2H) 3.55 (s, 3H) 3.2 (m, 4H) 2.5 (m, 4H) 2.25 (s, 3H)

From intermediate 17 and N-methylpiperazine

Example 14

N-[2-(*Iso*-propylamino)-1-methyl-1H-benzimidazol-6-yl] 2-(4-trifluoromethylphenoxy)-acetamide

LCMS (method A) retention time 6.66 min, ($M+H^+$) 407

^1H NMR (DMSO-d_6) d 10.0 (br s, 1H) 7.7 (d, 2H) 7.55 (s, 1H) 7.2 (d, 2H) 7.1 (d, 1H) 7.05 (d, 1H) 6.3 (d, 1H) 4.8 (s, 2H) 4.0 (m, 1H) 3.45 (s, 3H) 1.15 (d, 6H)

From intermediate 17 and *iso*-propylamine (microwave conditions, 220°C for 1h)

Example 15

N-[2-(3-Furyl)-1-methyl-1H-benzimidazole-6-yl] 2-(4-trifluoromethylphenoxy)-acetamide

A mixture of N-(2-chloro-1-methyl-1H-benzimidazol-6-yl) 2-(4-trifluoromethylphenoxy)acetamide (intermediate 17, 140mg), 3-furanboronic acid

(82mg), [1,1-bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with dichloromethane (1:1) (60mg) was dissolved in dimethylformamide and treated with an aqueous solution of cesium carbonate (2M, 548ml). The mixture was degassed and flushed with nitrogen then heated in the microwave at 130°C for 30 minutes. The mixture was partitioned between ethyl acetate and water and the organic layer was washed with water, dried ($MgSO_4$) and filtered. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica eluting with dichloromethane then increasing amounts of methanol up to a ratio of 49:1 to give N-[2-(3-furyl)-1-methyl-1H-benzimidazole-6-yl] 2-(4-trifluoromethylphenoxy)acetamide as a white solid (45mg).

LCMS (method A) retention time 6.46 min, ($M+H^+$) 416

^1H NMR (DMSO-d_6) d 10.3 (br s, 1H) 8.45 (s, 1H) 8.05 (s, 1H) 7.9 (s, 1H) 7.7 (d, 2H) 7.6 (d, 1H) 7.3 (d, 1H) 7.2 (d, 2H) 7.05 (s, 1H) 4.9 (s, 2H) 3.9 (s, 3H)

Example 16

N-[7-Methyl-5-(1-pyrrolidinyl)thiazolo[5,4-b]pyridin-2-yl] 2-(4-trifluoromethyl-phenoxy)acetamide

A mixture of 2-amino-7-methyl-5-(1-pyrrolidinyl)thiazolo[5,4-b]pyridine (intermediate 24, 25mg), 4-trifluoromethylphenoxyacetic acid (44mg), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (77mg) and *N,N*-diisopropylethylamine (88ml) in dimethylformamide was stirred at room temperature for 4h and then allowed to stand for 3 days. Water was added and the mixture was extracted with ethyl acetate, washed with water, saturated aqueous sodium bicarbonate solution, dried ($MgSO_4$), filtered and the filtrate was evaporated to dryness. The residue was purified by chromatography on silica, eluting with a mixture of dichloromethane and ethyl acetate (19:1) to give N-[7-methyl-5-(1-pyrrolidinyl)thiazolo[5,4-b]pyridin-2-yl] 2-(4-trifluoromethylphenoxy)acetamide as an off-white solid (18mg).

LCMS (method A) retention time 10.04 min, ($M+H^+$) 437

^1H NMR (DMSO-d_6) d 12.5 (br s, 1H) 7.7 (d, 2H) 7.15 (d, 2H) 6.45 (s, 1H) 4.95 (s, 2H) 3.4 (m, 4H) 2.5 (s, 3H) 1.95 (m, 4H)

By proceeding in a similar manner the following compound was prepared from the appropriate starting materials:

Example 17

N-{5-[N-(2-dimethylaminoethyl)-N-methylamino]-7-methylthiazolo[5,4-b]pyridin2-yl} 2-(4-trifluoromethylphenoxy)acetamide

LCMS (method A) retention time 6.48 min, ($M+H^+$) 468

^{1}H NMR (DMSO-d_6) d 12.4 (br s, 1H) 7.7 (d, 2H) 7.2 (d, 2H) 6.6 (s, 1H) 5.0 (s, 2H) 3.6 (t, 2H) 3.05 (s, 3H) 2.5 (s, 3H) 2.4 (t, 2H) 2.2 (s, 6H)

From intermediate 25 and 4-trifluoromethylphenoxyacetic acid.

The following assays may be used.

MCH-1R SPA

Chinese hamster ovary (CHO) cell membranes (5mg) overexpressing the MCH-1R (Euroscreen s.a.) were incubated with 25mg of wheat germ agglutinin SPA beads (Amersham Biosciences UK Ltd) and 0.4nM ^{125}I-[Phe^{13}, Tyr^{19}]-MCH (Amersham Biosciences UK Ltd) in a final volume of 100ml of binding buffer (25mM HEPES, 10mM NaCl, 5mM $MgCl_2$, 1mM $CaCl_2$, 0.1% BSA) containing 5mM phosphoramidon for 1 hour at room temperature. Non-specific binding was determined in the presence of 1mM (Phe^{13}, Tyr^{19})-MCH (Bachem (UK) Ltd). Bound ^{125}I-[Phe^{13}, Tyr^{19}]-MCH was detected using a MicroBeta TRILUX liquid scintillation counter (Perkin Elmer). Compound IC_{50} was determined using a 6-point dose response curve in duplicate with a semi-log compound dilution series. IC_{50} calculations were performed using Excel and XL fit (Microsoft).

Ca^{2+} Mobilization Assay

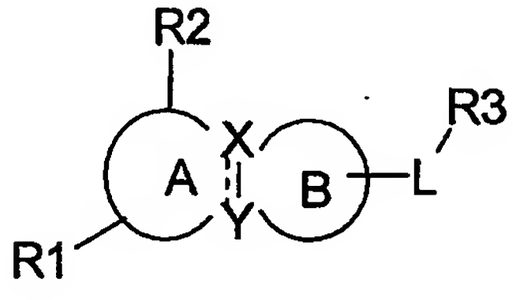
Stable CHO-K1 cells expressing the MCH-1R were seeded (35,000 cells per well with a plating volume of 50ml) into collagen-coated 96-well plates 24 hours prior to the assay. The cells were then loaded with a fluorescence-imaging plate reader (FLIPR) calcium kit dye (Calcium 3 kit, Molecular Devices Ltd) containing 5mM final concentration of probenecid and incubated at 37°C for 1 hour in a 5% CO_2 atmosphere. The fluorescence emission caused by intracellular calcium mobilization elicited by the agonist, (Phe^{13}, Tyr^{19})-MCH, of the expressed receptor was determined with a FLEXstation benchtop scanning and integrated fluid transfer workstation (Molecular Devices Ltd). To detect

antagonists and determine compound IC_{50}, compounds were pre-incubated at varying concentrations with the loaded cells for 15 minutes at 37°C, 5% CO_2, prior to the addition of the agonist at its EC_{80}. The fractional response values for each well were calculated as peak minus basal response. Results were calculated as the mean of triplicate wells using Excel and XL fit (Microsoft).

Compounds of formula (1) exhibit useful activity in the assays described above.

CLAIMS

1. A compound of structural formula (1):

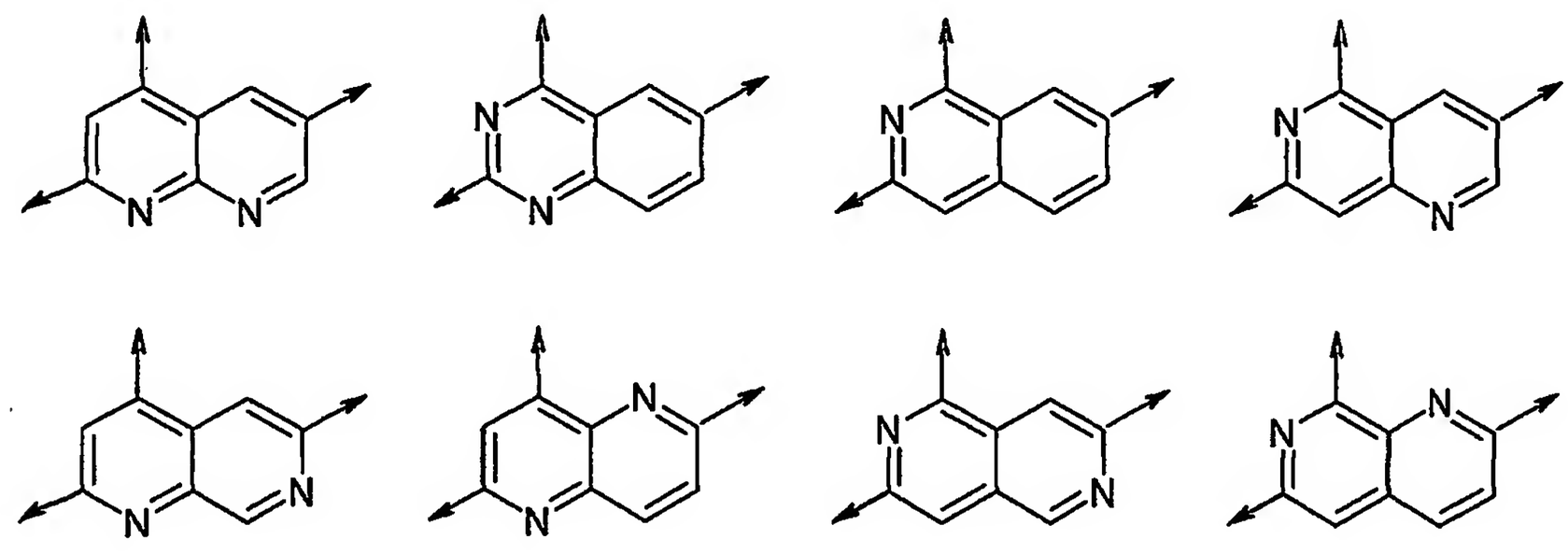


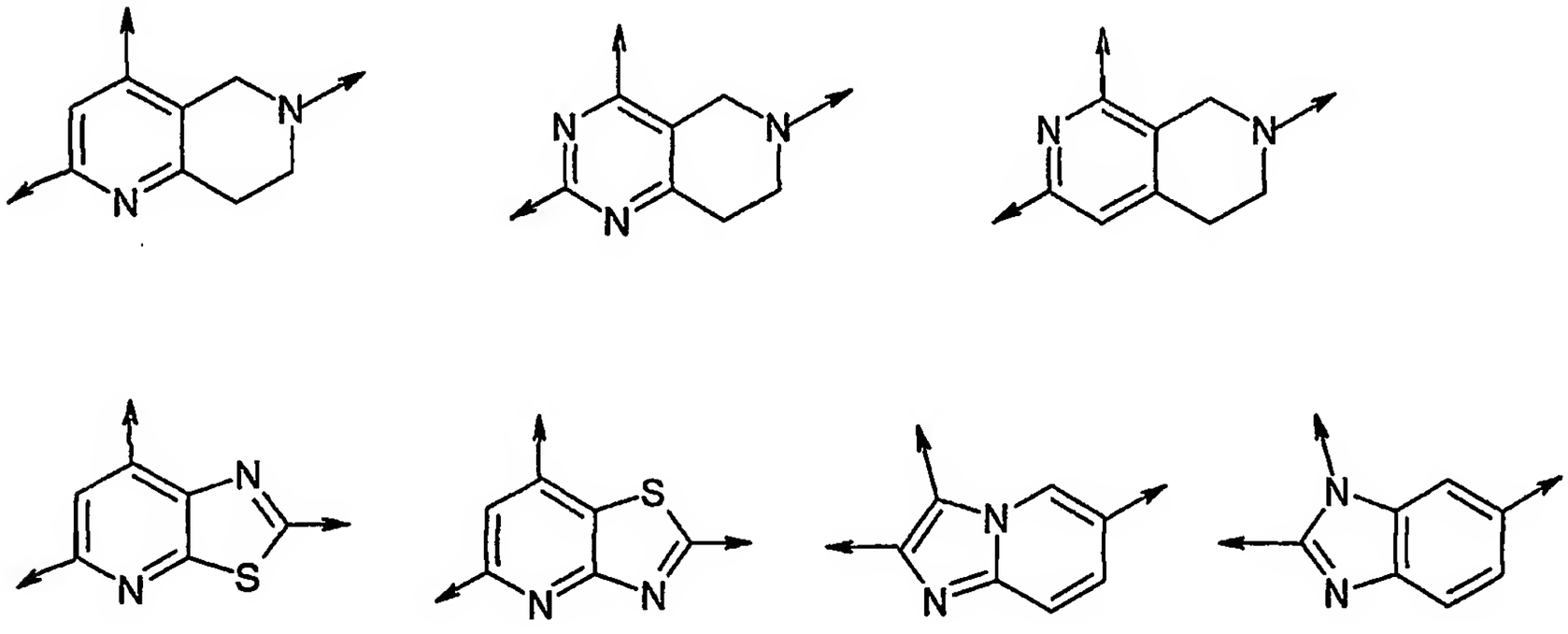
(1)

wherein X and Y each independently represent N or C;

---- represents a single or double bond;

the ring system represented by formula (1) includes the following, wherein the arrows indicate the position of attachment of the substituents:





R1 represents NR4R5 or optionally substituted aryl, heteroaryl, aryl-fused-cycloalkyl, heteroaryl-fused-cycloalkyl, aryl-fused-heterocycloalkyl or heteroaryl-fused-heterocycloalkyl;

R2 represents H, R6, alkyl or alkyl-R6;

R4 and R5, which may be the same or different, each independently represents H, alkyl, alkyl-R12, optionally substituted cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

R6 represents halogen, CN, CONR7R8, SO_2NR7R8, OR9, NR7R8, NR7COR10, $NR7SO_2R10$ or NR7CONR7R8;

R7 and R8, which may be the same or different, each independently represent H, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

R9 represents H, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

R10 represents alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl;

R3 represents optionally substituted aryl, heteroaryl, aryl-fused-cycloalkyl, heteroaryl-fused-cycloalkyl, aryl-fused-heterocycloalkyl or heteroaryl-fused-heterocycloalkyl;

L represents $-(CH_2)_nCON(R11)(CH_2)_m-$, $-(CH_2)_nSO_2N(R11)(CH_2)_m-$, $-(CH_2)_nCON(R11)(CH_2)_rO-$, $-(CH_2)_nSO_2N(R11)(CH_2)_rO-$, $-(CH_2)_nCON(R11)(CH_2)_rS-$, $-(CH_2)_nSO_2N(R11)(CH_2)_rS-$, $-(CH_2)_nCON(R11)(CH_2)_rN(R11)-$, $-(CH_2)_nSO_2N(R11)(CH_2)_rN(R11)-$, $-(CH_2)_nN(R11)CO(CH_2)_m-$, $-(CH_2)_nN(R11)SO_2(CH_2)_m-$, $-(CH_2)_nN(R11)CO(CH_2)_mO(CH_2)_p-$, $-(CH_2)_nN(R11)SO_2(CH_2)_mO(CH_2)_p-$, $-(CH_2)_nN(R11)CO(CH_2)_mS(CH_2)_p-$, $-(CH_2)_nN(R11)SO_2(CH_2)_mS(CH_2)_p-$, $-(CH_2)_nN(R11)CO(CH_2)_mN(R11)(CH_2)_p-$, $-(CH_2)_nN(R11)SO_2(CH_2)_mN(R11)(CH_2)_p-$, $-(CH_2)_nO(CH_2)_m-$, $-(CH_2)_nS(CH_2)_m-$, $-(CH_2)_nN(R11)(CH_2)_m-$, $-(CH_2)_nCO(CH_2)_m-$, $-(CH_2)_nSO_2(CH_2)_m-$, $-(CH_2)_q-$, $-(CH_2)_nCO(CH_2)_mO(CH_2)_p-$, $-(CH_2)_nSO_2(CH_2)_mO(CH_2)_p-$, $-(CH_2)_nCO(CH_2)_mS(CH_2)_p-$, $-(CH_2)_nSO_2(CH_2)_mS(CH_2)_p-$, $-(CH_2)_nCO(CH_2)_mN(R11)(CH_2)_p-$,

$-(CH_2)_nSO_2(CH_2)_mN(R11)(CH_2)_p-$, $-(CH_2)_n$-cycloalkyl-$(CH_2)_m-$, $-(CH_2)_n$-heterocycloalkyl-$(CH_2)_m$, $-(CH_2)_n$-aryl-$(CH_2)_m-$ or $-(CH_2)_n$-heteroaryl-$(CH_2)_m-$, and in each case, the linker may be attached either way round, i.e. the left hand end as drawn may be attached to the ring system and the right hand end to R3, or vice versa;

R11 represents H or alkyl;

R12 represents halogen, CN, CONR7R8, SO_2NR7R8, OR9, NR7R8, NR7COR10, NR7SO_2R10 or NR7CONR7R8;

n, m p each independently represent 0, 1 or 2;

q represents 0,1, 2, 3, 4 or 5;

r represents 2 or 3;

and corresponding N-oxides, pharmaceutically acceptable salts, solvates and prodrugs thereof.

2. A compound according to claim 1, wherein R1 is an optionally substituted heteroaryl group attached to the quinoline ring via a carbon or nitrogen atom.

3. A compound according to claim 2, wherein the heteroaryl group is pyridyl, furanyl, imidazolyl or pyrazolyl.

4. A compound according to claim 1, wherein R2 is NR4R5.

5. A compound according to any preceding claim, wherein R2 is alkyl or heteroalkyl.

6. A compound according to any preceding claim, wherein the ring system is quinazoline.

7. A compound according to claims 1 to 5, wherein the ring system is benzimidazole.

8. A compound according to any preceding claim, wherein R3 is para-substituted phenyl.

9. A compound according to any preceding claim, wherein L is *-$(CH_2)_nN(R11)CO(CH_2)_mO(CH_2)_p-$ or *-$(CH_2)_nN(R11)CO(CH_2)_m-$ and * is attached to the quinoline ring.

10. A compound according to claim 1, selected from:

N-[4-methyl-2-(1-pyrrolidino)quinazolin-6-yl] 2-(4-trifluoromethyl-phenoxy)acetamide

N-[4-methyl-2-(1-pyrrolidino)quinazolin-6-yl] 2-(4-chlorophenoxy)acetamide

N-{2-[N-(2-dimethylaminoethyl)-N-methylamino]-4-methylquinazolin-6-yl} 2-(4-trifluoromethyl-phenoxy)acetamide

N-[4-methyl-2-(1-pyrrolidino)quinazolin-6-yl] 2-(4-methoxyphenoxy)acetamide

N-[4-methyl-2-(1-pyrrolidino)quinazolin-6-yl] 2-(2-chlorophenoxy)acetamide

N-[2-(3-furyl)-4-methylquinazolin-6-yl] 2-(4-trifluoromethylphenoxy) - acetamide

N-[1-methyl-2-(1-pyrrolidino)-1H-benzimidazol-6-yl] 2-(4-trifluoromethylphenoxy)acetamide

N-[1-methyl-2-(1-pyrrolidino)-1H-benzimidazol-5-yl] 2-(4-trifluoromethylphenoxy)acetamide

N-[1-methyl-2-(1-pyrrolidino)-1H-benzimidazol-6-yl] 2-(4-trifluoromethyl-phenoxy)acetamide

N-[1-methyl-2-(1-pyrrolidino)-1H-benzimidazol-5-yl] 2-(4-trifluoromethyl-phenoxy)acetamide

N-[2-(1-pyrrolidino)benzimidazol-5-yl] 2-(4-trifluoromethyl-phenoxy)acetamide

N-{2-[N-(2-dimethylaminoethyl)-N-methylamino]-1-methyl-1H-benzimidazol-6-yl} 2-(4-trifluoromethylphenoxy)acetamide

N-{2-[N-(2-dimethylaminoethyl)-N-methylamino]-1-methyl-1H-benzimidazol-5-yl} 2-(4-trifluoromethylphenoxy)acetamide

N-[2-(4-methylpiperazino)-1-methyl-1H-benzimidazol-6-yl] 2-(4-trifluoromethylphenoxy)acetamide

N-[2-(*Iso*-propylamino)-1-methyl-1H-benzimidazol-6-yl] 2-(4-trifluoromethylphenoxy)acetamide

N-[2-(3-furyl)-1-methyl-1H-benzimidazol-6-yl] 2-(4-trifluoromethyl-phenoxy)acetamide

N-[7-methyl-5-(1-pyrrolidinyl)thiazolo[5,4-b]pyridin-2-yl] 2-(4-trifluoromethylphenoxy)acetamide and

N-{5-[N-(2-dimethylaminoethyl)-N-methylamino]-7-methylthiazolo[5,4-b]pyridin2-yl} 2-(4-trifluoromethylphenoxy)acetamide.

11. A compound according to any preceding claim, for use in therapy.

12. A pharmaceutical composition comprising a compound according to any preceding claim and an acceptable carrier or diluent.

13. The use of a compound according to any of claims 1 to 9, for the manufacture of a medicament for use in the treatment, prevention or suppression of a disease mediated by the MCH receptor.

14. Use according to claim 13, wherein the disease is selected from: obesity, diabetes, appetite and eating disorders, cardiovascular disease, hypertension, dyslipidemia, myocardial infarction, gall stones, osteoarthritis, certain cancers, AIDS wasting, cachexia, frailty (particularly in the elderly), binge eating disorders including bulimina, anorexia, mental disorders including manic depression, depression, schizophrenia, mood disorders, delirium, dementia, severe mental retardation, anxiety, stress, cognitive disorders, sexual function, reproductive function, kidney function, diuresis, locomotor disorders, attention deficit disorder (ADD), substance abuse disorders and dyskinesias including Parkinson's disease, Parkinson-like syndromes, Tourette's syndrome, Huntingdon's disease, epilepsy, improving memory function, and spinal muscular atrophy.

15. Use according to claim 14, wherein the disease is obesity.

16. Use according to claim 15, wherein the compound is for use in combination with an anorectic agent or a selective serotonin reuptake inhibitor.

17. Use according to claim 15 or claim 16, wherein the compound is to be administered in an amount of 0.01 to 100 mg per kg of a patient.

18. Use according to claim 13, wherein the disease is a condition selected from schizophrenia, anxiety, bipolar disorder and depression.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/004329

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D403/04 C07D413/04 C07D401/04 C07D513/04 C07D239/84
C07D235/30 A61P25/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CARPENTER AND HERZOG: "melanin-concentrating hormone receptor antagonists as potential antiobesity agents" EXPERT OPIN. THER. PATENTS, vol. 12, no. 11, 2002, pages 1639-1646, XP002318627 cited in the application whole document; especially compounds 1-16 plus references ---- -/--	1-18

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 February 2005	10/03/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schmid, A

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/004329

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LACOVA M ET AL: "Synthesis and biologicyl activity of 6-X-2-(4-R-phenoxyacetylamino)be nzothiazole derivatives" CHEMICK ZVESTI - CHEMICAL PAPERS, VEDA, BRATISLAVA, SK, vol. 38, no. 5, 1984, pages 693-698, XP009020806 ISSN: 0366-6352 table 1, compound III	1-10

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